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DOES GASTROSTAXIS EXIST AS AN INDEPENDENT DISEASE?

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IT is well known that profuse haemorrhage may occur from the mucous membrane of the stomach apart from gastric ulceration. For example, in severe anaemias, in infective disease, in purpuric conditions, and in toxaemias associated with diseases of the liver and kidneys, it is a common experience to find the mucous membrane of the stomach intact when vomiting of blood has occurred during life.

In the condition known as gastrostaxis, however, there is said to be an oozing of blood from the mucous membrane of the stomach not only in the absence of any ulceration of that organ, but also in the absence of any other disease in which bleeding is likely to occur. Gastrostaxis is also said to possess a definite clinical history simulating that of gastric ulcer—namely, pain, vomiting, and haematemesis occurring in attacks in either sex, but especially in young females. It seems to me that the actual existence of gastrostaxis as a common clinical entity is hardly established on a sufficiently sound basis, and that it is extremely important for the question to be definitely decided one way or the other, because it is obviously absurd to treat a case of gastrostaxis by operation, whereas in the haemorrhage of gastric ulcer life may often be saved by timely operative interference.

For some time my attention has been particularly directed to the difficulties in the way of proving that this disease exists, and my object in writing this paper is to emphasize these difficulties and to encourage others to pay especial attention to the condition of the stomach at all *post-mortem* examinations of patients who have died of haematemesis I am continually on the look-out for cases of gastrostaxis, but have never yet encountered such a condition on the *post-mortem* table, in all cases having found one or more acute gastric ulcers.

The evidence that gastrostaxis exists is threefold, namely: (1) That at certain *post-mortem* examinations of patients who have died of haematemesis no lesion has

been found in the stomach to account for the bleeding. (2) That at certain operations performed upon such patients an ulcer has not been found. (3) That gastrostaxis possesses a definite clinical history. I shall critically examine each of these statements in turn.

Haemorrhage from the mucous membrane of the stomach is due to one of two pathological conditions:

1. There is some lesion of the walls of the blood vessels, allowing of the escape of blood, which breaks through the surface of the mucous membrane into the cavity of the stomach. There are two distinct conditions of the mucous membrane produced:

(*a*) If the haemorrhage be profuse enough to kill the patient it is quite common to find at the autopsy multiple erosions of the mucous membrane. These erosions are quite superficial, the bases of the glands being preserved, and form slight depressions in the surface of the mucous membrane as if the latter had been lightly rubbed off with the finger. When the stomach is hardened in formalin they can hardly be seen by the naked eye unless there be any altered blood adherent to them, but they are easily recognized microscopically. These erosions are of no importance, except that they may help to keep up the bleeding, and they do not develop into ulcers because the stomachs of such patients are kept in the resting condition, the secretion of gastric juice being therefore at a minimum, and secondly, the gastric cells themselves are healthy, and there is no tendency towards their further digestion by the gastric juice.

(*b*) If the haemorrhage be not profuse the condition found after death, which is always due to the primary disease, is one of multiple small or large interstitial haemorrhages into the mucous membrane, with perhaps a little coffee-ground material in the cavity of the stomach. Such interstitial haemorrhages appear as black patches on the inner surface of the stomach, which on microscopic examination are seen to be portions of mucous membrane infiltrated with blood which has not escaped externally. These haemorrhages cause no symptoms, and the patient is fed in the usual way, with the result that the stomach is actively digesting, and the infiltrated patch of mucous membrane is digested owing to the destruction of the gastric glands, and removed, leaving an ulcer. These two pathological conditions occur quite independently, and constitute two distinct types; but there is no doubt that at the same time one may see all transitions and combinations in different cases.

2 The haemorrhage is a secondary event resulting from ulceration of the mucous membrane. The ulcer is the primary condition and the haemorrhage due to a secondary opening up of a blood vessel. There is a great deal of confusion with regard to the conception of what is an erosion and what is an ulcer, and the two names are sometimes applied to precisely the same condition.

Both the terms "ulcer" and "erosion" imply a loss of substance, and when the lesion is once formed, there can

hardly be a clear distinction between them, the difference being only one of depth. From the point of view of morbid anatomy, therefore, an erosion may be regarded as a superficial ulcer.

From the point of view of general pathology, we are not yet in a position to formulate precise definitions of these two conditions. I think it will be granted by all that serious haemorrhage will not occur as the result of an erosion, so that if a patient die from gastric haemorrhage any lesions which may be subsequently found in the mucous membrane, and which are microscopically proved to be erosions, must be a result of the haemorrhage, which is therefore the primary condition. The lesion must be examined microscopically, because, as I shall show later, fatal haemorrhage may occur from an ulcer which is so shallow as to be indistinguishable from an erosion by the naked eye. To whatever pathological condition the term "erosion" be restricted is immaterial, because it is quite obvious that if a small artery be opened up and death result from profuse haematemesis, the lesion extends to the submucous tissue or deeper, and should undoubtedly be called an acute ulcer. This is the class of case with which I am dealing in this paper. It is often stated by writers that a slight abrasion or erosion existed, in the centre of which a blood vessel had been opened. Such a lesion is undoubtedly an ulcer, and a great deal of misconception arises from the use of these ambiguous phrases.

When moderately stretched out at an autopsy the thickness of the stomach wall is about 4 mm., the mucous membrane being about 1 mm., so that an ulcer reaching to the muscular coat must necessarily look shallow and especially so in proportion as its area is large. This shallow appearance almost forces the observer to call the lesion an abrasion or erosion and to consider it as of little moment. I do not forget that much of the congestion of an acute ulcer probably disappears after death.

Acute ulcers vary in diameter from about the size of a split pea to an inch. Small acute ulcers and the scars of acute ulcers are very easily overlooked at *post-mortem* examinations, and an ulcer may be cut through in opening the stomach, and so obliterated. All writers agree upon this point, and I think there is no doubt that many stomachs have been described as being free from any evidence of ulcer owing to the employment of a not sufficiently minute method of examination. For such an investigation the stomach should be placed in warm water so as to relax the muscular coats, and first examined in front of a light for opacities in the mucous membrane. It should then be pinned out on a board after being moderately stretched, and the surface should be well washed with a camel-hair brush, and carefully examined all over by means of a lens. Even now a scar may be missed. The specimen should then be hardened for twenty-four hours in 5 per cent. formalin, and dried by washing in methylated spirit. Stellate scars can be much easier seen

in the dry state, and if the specimen be photographed they are seen with greater ease still. The radiating lines are exaggerated by the photographic plate.

Hardening in formalin, of course, takes the colour out of the specimen; but I am presuming that the specimen has already been examined in the fresh state and all information possible gained from the presence of blood. The scars of acute ulcers are not always stellate in form. The only evidence of a scar may be a slight opacity of the mucous membrane which is adherent to the muscular coat at that spot.

If the ulcer has perforated the muscular coat and been at all extensive, the resulting scar will be a small surface very slightly depressed below the surrounding mucous membrane, but otherwise looking quite like it. The surrounding mucous membrane may be slightly puckered or not. The scar is always very much smaller than the ulcer from which it has resulted, and it often tends to be oblong, or like a small fissure, and may be quite invisible till the stomach is stretched. The area of such a scar may be less than a fifth of that of the ulcer preceding it, as I have been able to show experimentally.

A point of the greatest importance is that in the centre of a scar of this kind, almost invisible itself, may be found a tiny opening leading into an artery. One such case was only recognized by a piece of blood clot which protruded from the hole; this clot had been tunnelled by the blood, and formed a tiny projection from the scar. It is not sufficiently widely known that profuse haemorrhage may occur from an ulcer which is almost healed.

The following three cases illustrate the fact that death from profuse haemorrhage may occur at any stage in the evolution or cicatrization of an acute ulcer.

CASE I.—*Haemorrhage from an Acute Ulcer in Its Fully Developed Stage.*

The patient was a servant, aged 30 years, who was admitted to University College Hospital on February 19th, 1908. She had no previous history of any stomach disease or indigestion. On the morning of the day of her admission she suddenly vomited half a pint of blood, and had five such attacks during the day. She was blanched and had a small feeble pulse of 120 in frequency, but was well nourished and apparently otherwise healthy. During the next two days she had three attacks of haematemesis, melaena occurring. The vomiting stopped, but the patient died on the sixth day of her illness. At the *post-mortem* examination an acute ulcer was found on the posterior wall of the stomach, situated 1½ in. to the right of the cardiac orifice and 1 in. below the lesser curvature. It was sharply punched out and extended to the muscular coat of the stomach. It was round in shape, ¾ in. in diameter, and looked quite shallow. In the centre of the base was an opening into a small artery.

CASE II.—*Haemorrhage from an Acute Ulcer Advanced in Healing.*

The patient was a man, aged 49 years, who felt a sudden pain in the abdomen whilst at work on September 3rd of last year. The pain was followed by faintness and the patient vomited up two quarts of blood, according to his own statement. He had

epigastric pain after food, which he still continued to take, the pain coming on either at once or two or three hours after ingestion, and he had melaena. Five days later he vomited up a pint of blood, and on the sixth day was admitted to University College Hospital. It was found that seven years previously he had been in the hospital. The notes of the case showed that he then had pain three-quarters of an hour after food in the epigastrium, but no haematemesis. The vomiting often relieved the pain, but not always. This attack of pain and vomiting lasted seven weeks, and the patient recovered.

During the seven intervening years he never had any pain or vomiting until the present illness, but he had what he described as a little indigestion on and off. From the third day after admission he was treated by immediate feeding as recommended by Lenhartz. He did well for two days and then suddenly vomited up 24 oz. of blood and died six days later, on the eighteenth day of the disease, after gastro-enterostomy had been performed. At the *post-mortem* examination an acute ulcer was found on the small curvature of the stomach at a distance of 2½ in. from the pylorus. It was irregularly circular in outline and 5 mm. in diameter. It was rapidly healing, the base was smooth and almost level with the surrounding mucous membrane, which showed puckering, and the edges of the ulcer were smooth and showed fine lines radiating on to the surface of the ulcer. In the centre was an open vessel which had bled. Near this ulcer was a stellate scar resulting from a healed acute ulcer of an earlier date. A tiny acute duodenal ulcer which was granulating was also present.

This case also illustrates, what is a well-known fact, that acute ulcers tend to recur in the same individual.

Such acute ulcers normally heal in a few weeks, exactly as they do in animal experiments. They may produce no symptoms; pain and vomiting without haematemesis may occur, or pain and vomiting with haematemesis. Sudden haematemesis or perforation without preceding symptoms constitute well-known clinical types of this disease.

CASE III.—*Haemorrhage from an Acute Ulcer almost Healed.*

The patient was a female, aged 69 years, who, after climbing up seventy stairs, was suddenly seized with nausea, and vomited up about an eggcupful of blood. On the following day (February 1st, 1910) she vomited a pint of blood, and was brought to University College Hospital. A fortnight before admission she had had a "bilious attack," and since then had pain in the stomach. Last August she had a similar attack without haematemesis. With the exception of these two attacks, separated by an interval of five months, she had no stomach disease at all. She vomited blood several times, and had melaena for the first five days, after which mouth feeding was commenced. She did well for four days. On the next day bleeding again commenced, and the patient died on the eighteenth day of the illness. At the autopsy four cicatrized acute ulcers were found on the small curvature of the stomach. Two of the cicatrices were stellate, and two were round, and in the centre of one of the latter was a tiny hole leading into a small vessel.

This case illustrates the occurrence of haemorrhage from an ulcer which is healed except for a small hole in the centre leading into the bleeding vessel. An interesting point about the case is that only two of the scars were found at the autopsy, the two remaining ones being found on the following day after drying the stomach as described above.

Before excluding acute gastric ulcer as the cause of haematemesis one ought, therefore, to exercise the greatest care, and be fully acquainted with all the conditions which are to be looked out for. Such cases as those I have quoted above are common enough, and all observers agree that they may be overlooked at the autopsy with the greatest ease The lesions are often called abrasions or erosions because they look so shallow, which is not surprising considering that the thickness of the mucous membrane of the stomach is only about 1 mm., and the base may be almost filled up, as these ulcers are often advanced in healing. The older physicians taught that bleeding might occur from the stomach in the absence of any ulcer, and many such cases were called "vicarious menstruation." Within recent times, however, Hale White[1] was only able to collect 10 cases from the literature, in which it was stated that no *post mortem* lesion was found to account for the preceding haematemesis; one of these cases was under the care of Dr. Hale White himself, who was unable to find any evidence whatever of ulcer, erosion, or bleeding point at the autopsy. This is in striking contrast with the large number of cases of haemorrhage due to acute ulcer which have been recorded, and which are so well known as not to need reference.

Turning to another aspect of the question, a second piece of evidence quoted in favour of the occurrence of gastrostaxis is the fact that several cases of haematemesis have been recorded in which the patients have been operated upon; the interior of the stomach examined during life, and no ulcer found. These cases fall into three groups: (1) Those in which no lesion whatever was found. (2) Those in which a single bleeding point was found. (3) Those in which multiple bleeding points were found. The first group contains the greatest number of cases.

From what I have said above, it will be at once evident that it is quite impossible to explore the interior of the stomach during life thoroughly enough to exclude the presence of an acute gastric ulcer or a scar left by such an ulcer.

Cases are recorded in which the stomach was found normal at operation and yet an ulcer discovered at the subsequent autopsy (Dieulafoy,[2] Stevens[3]).

The inability to find the lesion at an operation is therefore no evidence that an acute ulcer is not present.

If a bleeding point be found in the mucous membrane of the stomach at an operation, it appears to me very questionable whether the exact condition of such a lesion can be accurately made out, and therefore whether the operator is justified in calling it a mere erosion.

The ease with which the point can be examined at an operation depends upon its position, but still, considering the difficulty that is experienced in deciding upon the nature of the lesion by naked-eye appearances at an autopsy, it seems to me that such difficulty must be greater at an operation, whatever the position of the lesion, and that the depth could certainly not be judged

to a fraction of a millimetre. Such an operation must be done hurriedly, owing to the condition of the patient, and the bleeding must tend to obscure the character of the lesion.

My experience of operations on the human subject is, however, only that of a spectator, so that I cannot do better than quote the words of a surgeon[4] who has had considerable experience in such operations. After stating his opinion that the bleeding from an acute gastric ulcer is nearly always arterial in origin when it is severe, he goes on to say:

> During life the ordinary acute ulcer of the stomach usually takes the appearance of a linear or triradiate fissure, out of which the blood trickles in a steady, continuous stream. . . . *Post mortem*, when all the congestion and oedema have gone, the arteries, especially in a patient who has died from loss of blood, contract to such an extent that they appear to be quite insignificant in point of size, and a lateral opening, such as is usually present, is almost certain to be overlooked. Unless the blood vessels of the stomach are injected, or some special examination is made, the bleeding point is scarcely ever found in an acute ulcer, and the loss of blood is almost certain to be laid to the credit of the capillaries.

When the bleeding is slight, it comes from the capillaries or veins in the base of the ulcer. If such an ulcer be bleeding, it must be easier to find it in the living person than at an autopsy, but it must be more difficult to examine accurately. If any doubt exist with regard to the nature of a lesion after death, the question can be settled by microscopic examination. The statement, therefore, that a bleeding point is found at an operation certainly appears to me to be no more in favour of the case being one of gastrostaxis than of such a lesion being an acute ulcer. Neither is the finding of multiple bleeding points any evidence against acute ulcer, because acute ulcers are often multiple, and one would expect that in such cases an artery might be opened in one, and that in some the bleeding would be chiefly capillary and in others venous. A case is recorded in which twenty acute ulcers were found at an autopsy.[5]

Another piece of evidence given in favour of gastrostaxis being a clinical entity is that it possesses a definite clinical history. Thus, there are said to be three symptoms —pain, vomiting, and bleeding. These symptoms occur in attacks separated by intervals of months or years of freedom from any symptoms, or at most symptoms of indigestion may occur. These attacks may occur over many years. The first sign of the disease may be profuse haematemesis. The blood is bright red, and varies greatly in amount. In each attack blood is vomited on occasions separated by a few hours or days. The disease occurs in patients chiefly between the ages of 20 and 40 years, and affects females more than males. Vomiting and pain may occur without haematemesis.

I have not the slightest doubt in my own mind that a disease of this type exists, and also that it is commonly not chronic gastric ulcer, but in every case of this sort

which I have seen, and which has died, I have invariably found an acute gastric ulcer which has perforated a blood vessel. From the writings of other observers it is evident that they recognize these recurrent attacks as being due to acute ulcers, but I do not think that sufficient stress is laid upon the recurrences in descriptions of acute gastric ulcer in the textbooks.

In three cases within the last six months I have found the scars of old attacks, together with recent ulcers, which have caused death. There is no doubt that acute ulcers in the human subject heal in a few weeks, precisely as they do in animals, and that they are liable to recur in the same person. Each attack represents a new ulcer or ulcers, it lasts a few weeks at most, and the ulcers heal as in animals. I have been able to show that acute ulcers in animals may be delayed in their healing owing to motor insufficiency of the stomach leading to delayed emptying of that organ. In the same way an acute ulcer in man may be delayed in healing, as the following case shows:

A man, aged 34 years, was admitted to University College Hospital on August 28th of last year. The present illness had commenced about five weeks before admission with pain in the right side below the ribs. The pain was of an aching character and was said not to be related to food. He had a little vomiting, and on one occasion brought up a small quantity of blood, melaena occurring subsequently. He kept at his occupation, and one day whilst at work fainted, and shortly afterwards vomited a dark red clot of blood about the size of the fist. He had never had any indigestion nor gastric pain before the present illness.

Three days later he had two fainting attacks with melaena, and vomiting of blood on one occasion. He died five days subsequently, after gastro-enterostomy had been performed and after an illness of about seven weeks.

At the *post-mortem* examination the stomach was found to be dilated. An acute ulcer was present on the lesser curvature midway between the cardiac and pyloric orifices. It was oval in shape, measuring 8 mm. in its longest and 3 mm. in its smallest diameter. The edges were rounded, quite clean, and slightly incurved. The base was clean, and in the centre was a small eroded vessel which had caused the bleeding. A certain amount of thickening of the base had taken place, and puckering of the mucous membrane at the edges was distinctly visible. The ulcer was healing, but more slowly than normal and with more thickening. In short, the healing was delayed.

The ulcer, judging from the history, was probably at least seven weeks old. When an acute ulcer is delayed in the healing the epithelium grows over the surface more slowly than normal, and the glands are not so well regenerated. There is more dense fibrous tissue in the base than normally occurs, and more scarring results. It has been known for some time that acute ulcers following burns may only give rise to symptoms some weeks after the burns have healed, and unhealed ulcers have been found as long as two and a half months or more after this time. Such ulcers are undoubtedly acute ulcers produced at the time of the burn which have been delayed in their healing, or in which the healing has been completely stopped. It is quite likely that they have been slowly

extending, because perforation or sudden haemorrhage may occur as the first symptom. The importance of acute gastric ulcer, therefore, does not merely lie in the fact that it produces a definite group of symptoms during its formation and healing, but also that it may be delayed in its healing, or extend, and so form the initial stage of chronic gastric ulcer.

The natural conclusions to which one is driven from a consideration of the above points are that gastrostaxis as an independent disease is not yet indisputably proved to exist; and, on the other hand, that acute gastric ulcer is a most important and very common malady, and one which is worthy of more consideration than appears to be given to it.

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Further Observations on the Pathology of Gastric Ulcer. (Progress Report.)

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(From the Research Laboratories, University College Hospital Medical School.)

[PLATES 8 AND 9.]

The gastric ulcers in these experiments were produced by the injection of gastrotoxic serum. In a former communication (1) it was demonstrated that the serum, formed by immunising the rabbit with the gastric cells of the guinea-pig or with those of another rabbit, on injection into the guinea-pig's peritoneum produced general symptoms of intoxication and patches of necrosis in the mucous membrane of the stomach. In two later communications (2) and (3) the reactions of gastrotoxin *in vitro* and its precise mode of action *in corpore* were demonstrated.

In a fourth paper (4) the healing of gastrotoxic ulcers was dealt with, the method adopted in this series of experiments being that of injection of the serum directly into the stomach wall, so that it attacked the gastric cells directly and not through the blood stream, and in this way an ulcer was produced without general symptoms of intoxication. Briefly stated, it was found that such ulcers invariably healed within three or four weeks, and that, so long as the stomach emptied itself in the normal time, any moderate alteration in the acidity of the gastric contents did not delay the healing of the ulcers.

Chronic gastric ulcer in the human subject is, however, a common malady and, since ulcers formed by the process of self-digestion are initially acute, it was considered that there must be present some unknown condition or conditions which prevents the healing of such chronic ulcers.

The present communication deals especially with the effects of motor insufficiency of the stomach upon the healing of gastric ulcer.

In order to study the effects of motor insufficiency, it is necessary to use an animal which eats definite meals and has definite resting periods between. The cat was chosen as a suitable animal.

I. *Production of a Gastrotoxin Active against the Cat.*

1. *Method.*—The gastric cells of the cat were periodically injected into another animal, the blood of the latter gradually becoming poisonous for the cat's gastric mucous membrane. In this way I have endeavoured to immunise the rabbit, fowl, and goat. The rabbit and fowl proved very difficult animals to work with, as they very readily succumbed to the injections and could only resist very small doses.

Immunisation of the Goat.—I found that the goat was quite a suitable animal, and that it produced a very powerful gastrotoxin for the cat. Subcutaneous injections of cat's stomach cells were given at intervals of 7 to 10 days. The development of the immune substances in the blood of the goat is the same as I have before described in connection with the guinea-pig-rabbit gastrotoxin.

At first I injected the cells themselves, but found that abcesses were liable to result. I then tried an emulsion of cells in a solution of salicylic acid with a similar result. I now use a fresh dilute saline extract and give 50 c.c. for a dose. This very rarely produces suppuration if due care be exercised. The injections are given as I have described before, and the goat is bled from the ear if a small quantity of blood be required, but from the jugular vein with a cannula if a large quantity be needed.

I have used the blood serum so obtained as a means of producing an ulcer of a definite size and in a definite position in the cat's stomach.

2. *Effects of Local Injection of the Serum.*—The method of local injection into the cat's stomach wall is the same as I described in connection with the guinea-pig. The animal is anæsthetised with ether and the abdomen opened under antiseptic precautions. The stomach is drawn out and a hypodermic needle inserted between the mucous and peritoneal layers of the stomach. The serum is slowly injected with a 10-c.c. glass syringe. A local œdema is thus produced which forms a button-like thickening in the wall and projects into the lumen of the stomach as a rounded elevation.

If cut across, the fluid appears to be infiltrating the muscular coat. I have tried injections between the muscular and peritoneal coats and also between the muscular and mucous coats, but the result always appears to be the same, and I have not found it possible to destroy definite layers of the stomach wall in this way. It might be possible to do so in the case of a larger animal.

The amounts I have injected are from 5 to 10 c.c. I now employ 6 or 7 c.c. when I wish to produce an ulcer. The serum is rapidly absorbed, and apparently soaks into the overlying mucous membrane, which is then digested by the gastric juice. In all the following experiments the serum

was injected about the middle of the anterior wall at the cardiac end of the stomach. The animals, as a rule, do not eat well for a day or two, and may vomit once or twice and lose a little weight, but they soon recover and do not appear to suffer from any symptoms.

Formation.—The part of the mucous membrane affected sloughs, and by the third to the fifth day a clean ulcer results, which may involve the mucous membrane only, or may extend through the submucous and muscular coats. The depth depends upon the strength of the serum and upon the condition of the contents of the stomach. Perforation of the ulcer and resulting peritonitis occasionally occurs.

The acute ulcer so formed has cleanly defined margins and base, and is rounded or sometimes more irregular in shape. The whole of the area of muscular coat exposed may have disappeared or only a portion of it. In short, the ulcer presents the typical punched-out appearance of the acute gastric ulcer of man.

3. *Mode of Action of the Serum.*—As I have said, the action is a toxic one. The serum causes changes in the cells of the overlying mucous membrane, which is then digested by the gastric juice. That the action is not a mechanical one I have proved by injecting neutral fluids, as I have described previously in the case of the guinea-pig.

Ten cubic centimetres of cat's serum may be injected into the stomach wall, and whether the stomach is resting or digesting the serum is completely absorbed, and no ulcer results. Further, the effect produced on the stomach and the extent of the ulceration depend upon the stage of immunisation to which the goat has reached. So that there is a definite poison in the serum which directly affects the gastric cells in the same way as the guinea-pig-rabbit serum affects the cells of the guinea-pig.

4. *Dependence of the Extent of Ulceration upon whether the Stomach is Resting or Digesting.*—The necrotic lesions in the gastric mucous membrane being dependent upon the action of the gastric juice, it would appear that when the gastric glands were resting and the stomach empty the lesions should fail to appear or at all events be less marked than when the organ contained food, unless the gastrotoxin has the power of exciting secretion, a point which I have not yet investigated. I did a series of experiments on guinea-pigs, half the animals being starved and half fed, to settle this question, and found that I was unable to do so, because it is practically impossible in my experience to obtain a guinea-pig with its stomach absolutely empty. These animals will not live very long without food, and 24 hours after feeding the stomach contains a fair amount of highly acid fluid with food remnants.

In the case of the cat I have been able to prove definitely that when the stomach is empty the ulcer may not appear at all, and if it does that it only extends down to the submucous tissue, as a rule. Of nine experiments, ulceration failed to appear in three, and in the remaining six was only superficial. Even though the stomach be empty, there is often a little acid fluid in it, and this accounts for lesions occurring in the empty stomach.

I may point out also that the secretion of gastric juice not only depends upon the presence of food in the stomach, but is also a reflex nervous phenomenon. The cat has a very keen scent, and it is difficult to exclude the smell of food, which excites a flow of gastric juice. Moreover, I do not know how long the effect of the poison upon the cells lasts, and if food be given before this effect passes off, ulceration will of course occur.

This is a matter of no small importance, because when the process of ulceration is actively going on, one point in the treatment of such a case is obviously to stop the flow of gastric juice, not to encourage it by giving a diet such as recommended by Lenhartz (5); I have shown before that whenever the stomach contains food, even though the food be strongly alkaline, there is always a layer having a strongly acid reaction in contact with the wall of the stomach.

In all the following experiments, 15 grammes of cut-up meat were given to each cat two hours before the operation for the production of ulcer.

II. *The Healing of Acute Gastric Ulcer in the Cat.*

The healing stages have been studied in 21 cats on a normal diet. After the 3rd to the 5th day healing commences and is completed in many cases before, and nearly always by, the 21st day.

The edges of the ulcer are drawn together by contraction of the muscular coat of the stomach, and fixed in this position by the formation of fibrous tissue. Puckering of the surrounding mucous membrane is thus produced, and a stellate scar results. The amount of the puckering depends upon the previous degree of contraction of the muscular coat, and the shrinkage of the fibrous base of the ulcer (Plate 8, fig. 1). Sometimes the edges of the mucous membrane are curved inwards all round, probably by retraction of the muscularis mucosæ. The pressure of this edge interferes with the normal regeneration of the mucous membrane. The peritoneum is thickened to different degrees, and may be adherent to the omentum, liver, or diaphragm.

The regeneration of the gastric mucous membrane was fully worked out microscopically by Griffini and Vassale (6) 20 years ago. They cut off portions of mucous membrane, and found that the glandular epithelial cells proliferate

upwards to the surface, which they cover with flattened cells. These flattened cells grow out, and cover the whole raw surface by the 8th to the 10th day. The surface cells become cubical, and from them grow down tubes forming the new glands. Till the 30th day the glands are formed of cubical cells; at this time "pepsin cells" become differentiated at the base of the glands, and till the 55th day the glands increase in numbers. They make no mention of the development of oxyntic cells, but from a consideration of the figures in their paper I gather that they mean oxyntic cells by the term "pepsin cells." The above changes only occur at the stated times if the animal eat no food for four or five days at the beginning, and be then put on milk, and finally milk and bread for a time. If it be allowed to eat solid food at the beginning, regeneration has hardly commenced by the 8th to the 12th day.

The ulcers do not invariably heal in this rapid fashion, and in one case I found an unhealed ulcer on the 21st day. The microscopic investigation of this ulcer shows that its base is formed of dense fibrous tissue, which passes out on each side and blends with the muscular coats of the stomach. The edge of the mucous membrane on one side is recurved, but not on the other. At both edges the mucous membrane has grown out for a short space in a single layer of cells, and there ends at the edge of the ulcer.

The granulation tissue of the floor of the ulcer has fungated above the level of the regenerated mucous membrane, and this partially organised granulation tissue, for a depth of one-sixth of the whole thickness of the wall of the stomach, has undergone necrosis, the necrotic tissue extending up to the edge of the growing epithelium, where it stops. It is impossible for the cells to grow over this dead tissue, and hence the delay in the time of healing. This animal was fed on the same diet as the other twenty.

I have microscopically examined only one scar as old as 55 days.

The mucous membrane in this specimen is regenerated as described by Griffini and Vassale, but no oxyntic cells are present except at the very edge next to the normal mucous membrane. The mouths of the glands in places are dilated, and the glands widely separated by interstitial tissue.

The base of the scar is formed of loose fibro-cellular tissue, embedded in which are seen isolated strands of muscular tissue (fig. 2).

In another specimen, 41 days old, the base of the scar is formed of dense fibrous tissue, with thin and atrophied muscular tissue between it and the peritoneum. The edges of the normal mucous membrane are recurved. The regenerated mucous membrane is thin and the glands short, implanted directly on the fibrous tissue, and all dilated and lined by cubical cells. The mouths of the ducts are very wide. The interstitial tissue is excessive in amount and separates the glands widely. There are no central nor oxyntic

cells to be seen. At one edge the regenerated mucous membrane is connected with the normal mucous membrane by a single layer of cubical cells lying on the fibrous base of the scar. From the condition of the glands it seems as if this ulcer were delayed, but eventually healed up.

III. *The Production of Motor Insufficiency of the Stomach of the Cat.*

In speaking of the motor power of the stomach, I mean the ability of the muscular coats of the stomach to empty the contents into the duodenum Deficiency in this ability or motor insufficiency is seen clinically in different degrees. If the degree of motor insufficiency be judged by the size or capacity of the stomach, the more extreme conditions only will be observed, and the less extreme conditions, in which the size of the stomach is often not much increased, will be neglected. Increased capacity does not necessarily imply a pathological condition, for in health the stomach is an organ the size of which is subject to wide variations.

A very large stomach may not be a "dilated stomach" in the pathological sense. The whole question turns upon whether or not the muscular coat of the stomach is able to propel the food into the small intestine within the physiological limits of time, and the essential feature in motor insufficiency is a delayed expulsion of food from the stomach. The slighter grades depend upon a so-called atony of the muscular coat, and in such a condition the motor function may be so damaged that food is retained for 24 hours or more, or probably upon a temporary spasm of the pylorus in some cases; the higher grades, in which complete stagnation occurs, depend upon pyloric obstruction.

The commonest form of indigestion of food is probably chiefly associated with delay in the emptying of the stomach. It is such a condition that I have endeavoured to reproduce experimentally.

Method.—My method of estimating the presence and the degree of motor insufficiency existing is the same as that employed clinically, namely, that of finding out whether food remains in the stomach beyond a certain time, with the difference that clinically one passes the stomach tube. In these cases to be absolutely exact I kill the animal.

After a meal of 100 to 120 grammes of meat, the cat's stomach is usually empty in 12 hours. Cannon (7) found this by the employment of the X-rays after Bismuth meals; I have confirmed it by killing a series of animals at different times. So that if a cat be given a meal of 100 to 120 grammes of meat at 6 P.M. its stomach should be empty by 9 A.M. on the following morning; if not, it is the subject of motor insufficiency of the stomach.

The method of producing motor insufficiency which I employ is that of artificial pyloric stenosis.

The constricting band consists of a piece of rubber tubing as used for constricting the vena cava in my experiments on cardiac dropsy (8). The rubber tubing ($\frac{1}{4}$ inch or less in length) is slit open longitudinally and a silk ligature passed round the outside of it; each free end of the ligature is made to pierce the rubber tubing from without in and again from within out, the ligature now appearing just outside the cut margin. When the ends of the ligature are tied the cut margins come together and the lumen of the tube is restored. By taking a tube of appropriate diameter a thin-walled vessel such as a vein may be constricted to any definite fraction of its diameter required. This cannot be done exactly in the case of the duodenum, because its walls are too thick and it is a contractile organ, so that I have been unable to measure definitely the amount of constriction. The duodena of different cats vary enormously in diameter: a small cat may have a large duodenum and, *vice versâ*, a large cat a small duodenum; one has therefore to keep a supply of different sizes of tubes ready at each operation. I have found this method completely successful, but since one cannot measure the amount of constriction the latter has to be guessed, with the result that it is impossible to be absolutely certain what will happen in any given case. If too tight the animal will die, if too slack complete compensation occurs, but in most cases some degree of motor insufficiency results, and after a little practice this end can be accomplished in the vast majority of cases. The abdomen is opened in the middle line under strict antiseptic precautions, and the rubber tubing applied just beyond the pylorus around the first part of the duodenum.

The animals with motor insufficiency have diminished appetite and lose flesh; they occasionally vomit, but, curiously enough, vomiting may be practically absent in the higher grades of retention of food, possibly due to depressed sensibility of the sensory nerves of the stomach. In the slighter grades there is a delay in emptying the stomach, and in these there may be slight dilatation of the stomach or not; at all events the muscular coat has diminished resistance to stretching after death. A curious feature in these cases is the amount of hair found in the stomach. Hair is always liable to be found in the cat's stomach, due to the animal's habit of licking. In cases of motor insufficiency the hair collects in the stomach, as apparently it is not so able as food to pass the pylorus. The meat is cut up for the animals, as they will not usually eat large pieces. The amount of the appetite is easily estimated by weighing everything the animal is given and everything it leaves. In the higher grades of insufficiency the stomach is usually found

dilated and thinned, and may contain large quantities of brown acid fluid. On the other hand, the stomach may be found empty when vomiting has been a prominent symptom. In the latter cases retention of food is probably largely absent, as what remains is vomited. The animal may discover exactly how much its stomach is capable of dealing with within the physiological limits of time, so that no retention occurs. The presence of diminished appetite, vomiting, and wasting are therefore not definite indications of retention of food. The only tests which are of value are the presence of food in the stomach a certain length of time after a test meal, or the presence of dilatation of the stomach.

IV. *The Effects of Motor Insufficiency upon the Healing of Acute Gastric Ulcer in the Cat.*

The pylorus is first constricted and, after the animal has recovered and settled down to a more or less definite diet, a gastric ulcer is produced as described above on the anterior wall of the stomach, midway between the cardiac and pyloric orifices.

There are four groups of experiments.

Group I. Six experiments:—

Cat 1: weight 2865 grammes.

February 4, 1909.—Pylorus constricted. Tube, 9 mm. Vomited twice; appetite soon recovered and in a few days eats an average of 250 grammes daily; no vomiting.

February 19.—Intramural injection of 6 *c.c. serum*.

March 11.—Test meal, 120 grammes meat at 6 P.M., all eaten. Weight 3105 grammes.

March 12.—Killed 9 A.M.; stomach empty except for considerable amount of hair. Acid in reaction. Scar of healed ulcer present (21*st day*) (fig. 3, A). This animal is useful as a control, as no motor insufficiency was present.

Cat 2: died the *day after* the serum was injected.

Cat 3: weight 3700 grammes. February 4, 1909.—Pylorus constricted. Tube, 9 mm. Vomited once or twice; appetite recovered, and in a few days eats 100 to 150 grammes. Weight 2895 grammes.

February 19.—Intramural injection of 6 *c.c. serum*. Appetite lost at first, but in a few days recovered to the extent of about 130 grammes a day, and then gradually lost again, and finally eats 10 to 30 grammes a day only; no vomiting.

March 11.—Test meal, 6 P.M., not eaten. Weight 2500 grammes.

„ 12.—Killed 9 A.M., stomach much dilated, wall thin and it main-

tains its shape on opening. Contains 160 c.c. brownish mucoid fluid containing 0·259 per cent. HCl. Large ulcer healing, base somewhat thickened and composed of granulation tissue on free surface (*21st day*).

Cat 4: died on the *eighth day* after the injection; 20 c.c. yellowish acid fluid in stomach, which was not dilated. An ulcer was present about the same size as that of Cat 6 in a sloughing condition.

Cat 5: weight 3610 grammes. February 10, 1909.—Pyloric constriction. Tube, 9 mm. Soon recovered and appetite good. Able to eat 200 grammes a day.

February 19.—Intramural injection of 6 *c.c. serum*. Appetite never bad, easily eats 200 grammes. Vomited once.

March 25.—Test meal, 105 grammes, 6 P.M. Weight 4270 grammes.

March 26.—Killed 9 A.M. Stomach distended and contained 80 grammes meat and some hair. An unhealed ulcer present, the base being formed of granulation tissue with a little hæmorrhage from it. Base thickened and omentum adherent to it. Feels like a thick nodule of fibrous tissue in the stomach wall (*35th day*) (fig. 3, B).

Cat 6: Died on the *third day* after injection; a large perforation present.

Group II. Eight experiments.—The pylorus was constricted in each animal, and on April 28, 1909, 8 *c.c. immune serum* of the goat were injected into the stomach wall of each. Six of these animals died within 10 days; of these, three had large ulcers, two perforated, and one had a large ulcer with extensive hæmorrhagic infiltration and ulceration of the mucous membrane around.

This extensive ulceration, with or without hæmorrhagic infiltration spreading round the ulcer, I have found in six cases of pyloric stenosis, and never apart from it. In all the cases the fluid in the stomach was neutral or alkaline. Occasionally there is some œdema of the stomach wall. It is possible that this condition may be due to a secondary bacterial infection owing to the alkalinity of the stomach contents, but this point remains to be investigated. The stomach contents, however, may be alkaline in the absence of this spreading ulceration.

Of the two remaining animals, one died on the 26th day with a large unhealed ulcer and the stomach a little dilated and thinned, and the other survived and was killed on the 56th day. The stomach of the latter animal was not dilated and it had disposed of its test meal of 60 grammes in 15 hours. There was a large triangular depressed scar with some contraction of the stomach at that spot. *Microscopical examination*: The base of the original ulcer is formed of young fibrous tissue composed of elongated cells and short fibres interlacing in every direction and packed together into

a dense mass. The newly formed mucous membrane is directly implanted on this fibrous tissue. There is no recurving of the normal mucous membrane. The newly formed glands are largely made up of cubical or columnar epithelial cells, but at the base in many places central cells have been formed, but no oxyntic cells. The glands mostly have distinct lumina and a large number of cystic spaces has been formed, the cysts being lined by flattened cells. The mouths of the glands are wide open and in many places a coarsely villous appearance is given to the surface (fig. 4). A great deal of cellular infiltration exists between the glands and in places projections of fibrous tissue from the base cut up the mucous membrane. In some of the large cysts ridges of fibrous tissue covered with epithelium project into the lumina, partially dividing them into locculi. Of the controls, two died with large ulcers during the first week and the remaining one was killed on the 55th day, showing the usual radiating scar of normal healing.

Group III. Seven experiments.—The pylorus was constricted in each animal, and on May 14, 1909, 6 *c.c. immune serum* of the goat were injected into the stomach wall of each. Six of these animals died within five days; of these, four had hæmorrhage infiltration and ulceration around the ulcer, which had been produced, and in one of these cases the ulceration occupied half the whole area of the mucous membrane of the stomach. In each case the fluid in the stomach was alkaline or neutral. Of the remaining two, one perforated and the other had an ulcer of the usual size. One of the animals survived and was killed on the 41st day. There was a little dilatation, and a small unhealed ulcer was present. This was to some extent concealed by the surrounding mucous membrane, which was very exuberant. *Microscopical Examination*: The edges of the normal mucous membrane are turned in, the mouths of the glands almost touching the thin epithelium covering the healed portion of the ulcer. The whole thickness of the stomach wall at this spot is composed of dense, sclerotic, fibrous tissue, with round cells in spaces here and there. In the centre is an unhealed portion occupying about one-fourth of the diameter of the original ulcer. The base of this unhealed portion is formed of looser tissue, containing cells and a few dilated capillary vessels, and in the centre this tissue projects and has undergone necrosis. The base of the original ulcer is much thicker in the centre than at the sides. There is another unhealed portion towards the side, about one-fourth the size of the former, where the recurved mucous membrane touches the base of the ulcer. The reformed epithelium covering the healed portion consists of a single layer of cells, apparently a continuation of that covering the surface of the normal epithelium. The cells are columnar in type, and as they near the

edges of the two ulcerated surfaces gradually become flatter and flatter till they look like endothelial cells and disappear (fig. 5). The cells are implanted directly upon the fibrous tissue of the base. At one spot two tiny gland ducts have started to grow, each consisting of a dozen or more cells and forming little depressions in the fibrous tissue, otherwise the reformed epithelium consists merely of a single layer of cells.

Of the control animals, one perforated on the 10th day and the other was killed on the 41st day and showed a small triangular scar in the stomach.

Group IV. Eight experiments.—The pylorus was constricted in each animal and on June 4, 1909, 5 *c.c. immune serum* of the goat were injected into the stomach wall of each. Four of these animals died within the first 15 days. Of these, one perforated, one had hæmorrhagic infiltration and ulceration around the ulcer, and two had ulcers of the usual size.

The remaining four cats survived and all had the scars of healed ulcers. Of these, two must be excluded because the stomach had been able to compensate and no motor insufficiency developed. The remaining two, whose autopsies were performed on the 52nd and 55th days respectively, and which had motor insufficiency, remain to be considered.

52nd Day Cat.—The base of the scar is formed of dense fibro-cellular tissue, at the outer part covered with a thin layer of atrophied muscle. The edges of the normal mucous membrane are recurved and where they press on the base of the scar have flattened the newly formed epithelium so that at one spot it only consists of a single layer of cubical cells. The new epithelium covering the scar has grown up into glands in the centre, where it is freed from pressure. The glands are formed entirely of duct epithelium directly implanted on the fibro-cellular tissue. There are no central nor oxyntic cells present. There is a good deal of cystic dilatation at one side where the normal joins the new mucous membrane. These cysts are lined by flattened epithelium. There is a considerable amount of new connective tissue between the glands.

55th Day Cat.—The base of the scar is not formed of such dense fibrous tissue as in the former cat, and the muscular coats of the stomach have not been destroyed to the same extent. The mucous membrane is thicker and the glands fairly well formed, central cells are present at the base and in places oxyntic cells can be seen. The glands are of irregular shapes and separated by infiltration of new connective tissue. There is some cystic formation of the glands.

The two control animals both lived and showed the radiating scars of normal healing on the 55th day. Sections of one showed the mucous

membrane completely reformed as I related in describing the normal healing of acute gastric ulcer.

In *Group I*, Experiments 1, 3, and 5 are conclusive. In Experiment 1 there was no motor insufficiency and the ulcer healed in the usual way, leaving a small stellate scar, within 21 days. In Experiments 3 and 5 there was motor insufficiency and the ulcers were unhealed on the 21st and 35th days respectively. Experiments 2, 4, and 6 are of use as controls to show what the ulcers were like in the early stages.

In *Group II* the 26th day animal had motor insufficiency and an unhealed ulcer. The 56th day animal showed a scar with considerable fibro-cellular thickening and imperfectly formed glands. The fibrous thickening and imperfect glands show a delay in the healing, but I have not included this case because I was unable to prove that there was motor insufficiency, the animal having 15 hours in which to dispose of its 60 grammes of food, although I think that it was present.

In *Group III* the 41st day animal had an unhealed ulcer and motor insufficiency. There was dense fibrous thickening of the sclerotic type and the mucous membrane which was reformed consisted of a single layer of cells such as should be present on the 8th or 10th day of normal healing according to Griffini and Vassale.

In *Group IV* the 52nd day cat had a scar of considerable fibro-cellular thickening covered with a mucous membrane composed of very imperfectly formed glands such as should be present on the 16th day of normal healing. The 55th day cat had a scar the base of which was not so dense, and the glands were almost completely reformed.

It is quite evident from these experiments that retention of food produced by motor insufficiency may delay the healing of an acute gastric ulcer for a period at least twice the length of the normal. Different degrees of insufficiency produce differences in the amount of delay.

The delay occurs at two stages:—

(1) When a single layer of epithelium covers the base of the ulcer and before glandular formation has commenced (= 10th day of normal healing).

(2) When the glands have been reformed but the central and oxyntic cells not differentiated. The glands are merely formed of duct epithelium at this stage (= 16th day of normal healing).

Whether, if the animals had been allowed to live, completely formed glands would have eventually developed is a very interesting question. In the normal healing of an ulcer there may be some delay, as is seen from the two cases quoted above, in which one was delayed owing to necrosis of the granulation tissue at the base of the ulcer, and the other was healed, but

covered with glands of the duct epithelium type. So that the delay occurring in cases of motor insufficiency is merely an exaggeration of the delay which may occur in exceptional cases normally. That it is a true delay is obvious, because the different conditions found exactly correspond to the various stages in the normal healing of an ulcer.

Cause of the Delay in Healing.—For the normal regeneration of the mucous membrane to take place it is necessary (1) that the epithelial cells should be uninjured and free to grow over the base of the ulcer; and (2) that the base of the ulcer should consist of healthy granulation tissue containing an abundance of cells, so that the over-growing epithelial cells can be properly nourished, and so that the tissue over which the cells grow can supply a suitable stroma for the growth of the glands from the surface epithelium. If either of these conditions be not fulfilled the healing must be delayed.

It will, I think, be generally admitted that the epithelial cells are more resistant to the action of the gastric juice than the tissue forming the base of the ulcer, and the great resistance displayed by these cells is seen in the promptitude with which they cover the surface, and by the fact that they can resist the action of HCl of 0·7 to 0·9 per cent. strength (4). Of course, the incurving of the mucous membrane at the edges of the ulcer must offer a formidable resistance to the growth of the cells, both by the abnormal direction in which the cells have to grow, and the pressure exerted on the base of the ulcer by the incurved mucous membrane. Still, this is by no means an insuperable obstacle, as the cells are readily able to grow round the angle in a single layer and, when free from the pressure, to sprout out into glands in the centre of the ulcer. So that one is rather compelled to look for any conditions which may be present in the *base of the ulcer* which can prevent the epithelium growing over it or are able to modify its growth. If the base of the ulcer be necrotic, as may occur as the result of bacterial invasion or digestion by the gastric juice, it is obvious that the growth of the epithelium over it would be at once arrested; and, on the other hand, if the base be irritated and dense fibrous tissue rapidly formed, it is equally obvious that the epithelium would be modified in its growth, both by deficient blood supply and the failure of the fibrous tissue to form a suitable stroma for the process of glandular formation. In the three cases described in the normal healing of ulcer, I have mentioned that in one the exuberant granulations had become necrotic and had stopped the growth of the epithelium; that in another the base was formed of dense fibrous tissue and the overlying glands formed of duct epithelium only; and that in the third the glands were completely regenerated and the underlying tissue more loose and cellular in character.

In the cases of pyloric stenosis the same principle is observed. In

proportion as the base is sclerotic the more difficult is it for the epithelium to be regenerated and the glands to proliferate. It follows from this that *the delay in the healing of an acute gastric ulcer is not so much due to a fault in the epithelium as to the condition of the base of the ulcer over which it is growing.*

It was shown by Griffini and Vassale, as stated above, that the base of a defect in the mucous membrane is covered with surface epithelium in 8 to 10 days if the animal eat no food for 4 to 5 days and is then put on milk, but that regeneration of the epithelium has hardly commenced by the 8th to 12th day if it eat solid food from the first day. The condition of the gastric contents is therefore of supreme importance in the healing of ulcer. In pyloric stenosis, food saturated with gastric juice is retained beyond the normal time. Excessive irritation and injury of the base of the ulcer results and bacteria have more time in which to attach themselves to it, so that in the early stages excessive exudation of leucocytes and perhaps necrosis of the granulation tissue results, and in the later stages excessive fibrosis. The former condition will delay the growth of the surface epithelium over the base, and the latter will prevent the regeneration of the glands. This appears to me to be comparable to the failure of cancer to grow in an immune mouse, the latter being unable to furnish a vascular stroma for the cancer to develop in (9). It is conceivable that excessive formation of sclerotic tissue in the base of the ulcer might completely prevent the growth of epithelium over it in which case the ulcer would deepen from digestion of the fibrous tissue, but of this I have no actual proof. Simple motor insufficiency will *delay* the healing of an acute ulcer, but will not *stop* the healing nor *make the ulcer extend.*

8. *Effect of Motor Insufficiency upon the Size of the Ulcer.*—A comparison of the sizes and tendency to perforate of the ulcers produced in the above cases of pyloric stenosis with those of the control animals shows that motor insufficiency has no influence in increasing the sizes or tendency to perforate of the ulcers produced.

On the other hand, in 6 out of 29 cases there were considerable haemorrhage and acute ulceration around the spot where the ulcer was produced, and in all these cases the gastric contents were alkaline or neutral. This is undoubtedly a direct result of the pyloric stenosis, as I have never seen it apart from that condition. Whether or not it is due to a secondary bacterial invasion of the ulcer, I am not at present in a position to state.

V. *Conclusions.*

1. A gastrotoxic serum active against the cat may be prepared by immunising the goat with cat's gastric cells.

Its properties, which have been examined, have been found to correspond to those of the gastrotoxin formed by immunising the rabbit with guinea-pig's gastric cells.

2. Acute gastric ulcer in the cat heals within a few weeks, as in the case of the guinea-pig. This result agrees with those of other observers who have produced lesions by injury of the gastric mucous membrane of dogs.

3. The ulceration produced by gastrotoxin is more extensive if produced whilst the stomach is digesting than whilst it is resting; in the latter case ulceration may fail to appear.

4. Motor insufficiency of the stomach definitely delays the healing of gastric ulcer for at least twice the normal time. There is more thickening of the base and less complete regeneration of the gastric glands than occurs in cases of normal healing. This may explain the beneficial effect following gastro-enterostomy for chronic gastric ulcer in man.

5. The character of the mucous membrane covering the base of an ulcer, in which the healing has been delayed, varies in proportion to the delay. It may consist of a single layer of epithelial cells on the 41st day, such as should be found on the 8th to the 10th day of normal healing; of regenerated glands consisting merely of duct epithelium on the 52nd day, such as should be found on the 16th day; or of almost completely regenerated glands. Whether eventually in process of time the glands would be always completely reformed has not been determined, but more likely they would not.

6. The delay in the healing in cases of motor insufficiency is due to a fault in the base of the ulcer, such as may occasionally be seen in normal healing. This fault may be due to necrosis of the base of the ulcer or excessive formation of sclerotic tissue therein, such conditions being the result of the low resistance which the connective tissues possess to digestion by the gastric juice, or possibly in some cases to a secondary bacterial infection.

7. When pyloric stenosis is present, extensive ulceration may be found around the ulcer, probably due to a bacterial infection. The ulcer actually produced by the serum, however, is no more liable to perforate nor to be more extensive than in the control animal.

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DESCRIPTION OF PLATES.

Plate 8.

Fig. 1.—To illustrate the normal healing of gastric ulcer in the cat.

A. Fourth day.—A punched out ulcer, with cleanly cut edges, extends through the muscular coat of the stomach.

B. 16th day.—This specimen shows an excessive amount of contraction, which is unusual. In the centre is a small unhealed surface.

Fig. 2.—Section of cat's stomach showing regeneration of the glands on the 55th day. The glands are irregular, no oxyntic cells are present, and there is a considerable amount of interstitial tissue.

Plate 9.

Fig. 3.—To illustrate the delay in healing produced by motor insufficiency of the stomach.

A. Stomach of control cat, Group 1. (Pyloric stenosis.) A small radiating scar is seen (21st day) to the right of the centre.

B. Stomach of Cat 5, Group 1. An unhealed and thickened ulcer is present (35th day). The stomach is a little dilated and the rugæ are not so prominent as normal.

Fig. 4.—Section of stomach of 56th day cat, Group 2. (Pyloric stenosis), showing very irregular growth and cystic dilatation of the regenerated glands.

Fig. 5.—Section of stomach of 41st day cat, Group 3. (Pyloric stenosis), showing an unhealed ulcer with sclerotic base and the epithelium growing over it in a single layer of cells.

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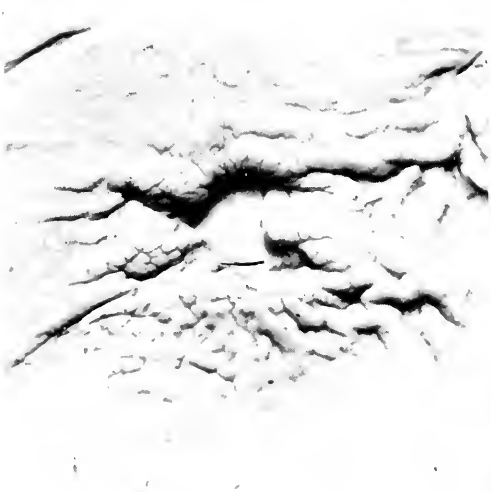

FIG. 1, A.

FIG. 1, B.

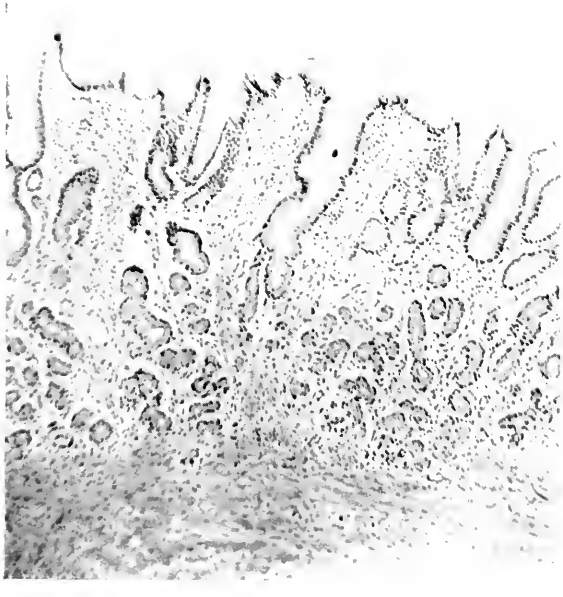

FIG. 2.

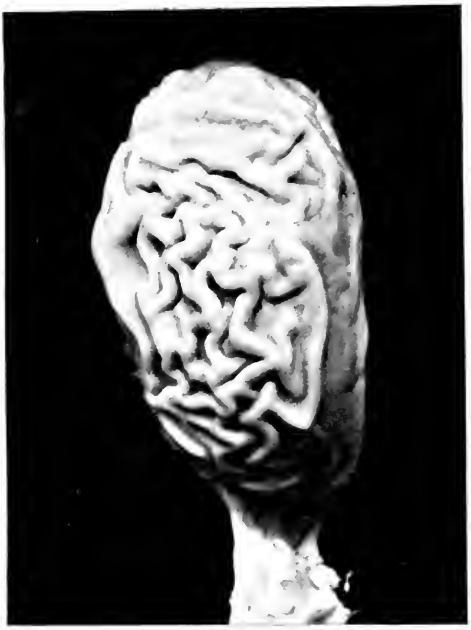

FIG. 3, A.

FIG. 3, B.

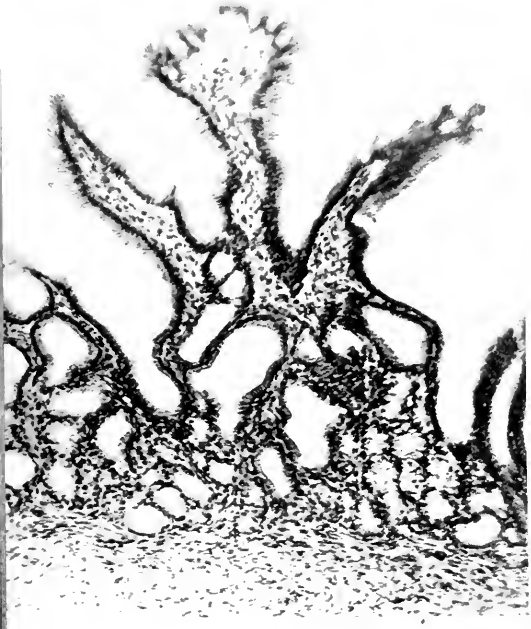

FIG. 4.

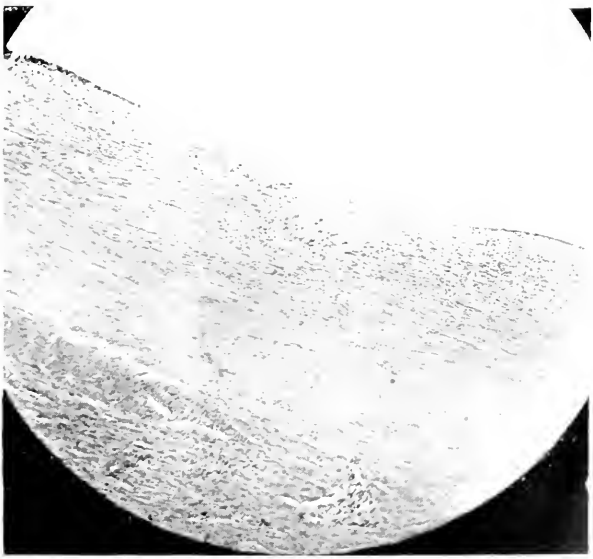

FIG. 5.

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GALVANOMETRIC CURVES YIELDED BY CARDIAC BEATS GENERATED IN VARIOUS AREAS OF THE AURICULAR MUSCULATURE. THE PACE-MAKER OF THE HEART.*

By THOMAS LEWIS.

(*From University College Medical School.*)

The observations upon which the present communication is based have been of two kinds, experimental and clinical. The results of the examination of a number of patients, and a number of animals under experimental conditions, are described side by side†.

The normal heart beat originates, as will be subsequently demonstrated, in the neighbourhood of the junction of superior vena cava and right auricle. The contraction travels from this point by a channel as yet indeterminate to the tissue uniting auricle and ventricle (the auriculo-ventricular bundle), and it is thence propagated by means of the bundle, its branches and the arborisations and network of the Purkinje system to the main mass of the ventricular musculature. The normal and regular rhythm of the heart may be disturbed, as is now universally recognised, by contractions dependent upon pathological impulse formation in the heart wall. And, as may be shown by mechanical records from auricle and ventricle, such impulse formation may have its seat in auricle, in ventricle, or in the tissues uniting the two chambers. The present paper is confined to a further discussion of such impulse formation in the auricle, for by galvanometric methods a closer identification of the seat of such impulse formation is possible.

As the normal heart beat consists of an auricular and ventricular systole, so the normal electrocardiogram is composed of two distinct portions, one dependent upon the auricular the other upon the ventricular contraction. An ectopic‡ auricular contraction is similarly portrayed by auricular and

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† In all the figures, experimental and clinical, the leads have been from right upper and left lower extremities.

‡ I use the term "ectopic contraction" to designate contractions arising in any portion of the musculature other than that lying in the neighbourhood of the superior cavo-auricular junction, and include contractions of the whole heart, or of auricle or ventricle alone where the contraction is not propagated from one chamber to the other.

It is essential that it should be observed that the definition covers not only the premature beat hitherto frequently designated as extrasystole, but is also intended to include contractions of a distinct nature; for example, the beats of an ideoventricular rhythm (the true ventricular

ventricular electric complexes, and it is to the characters and variations which obtain in these complexes, as they are found associated with pathological beats arising in the auricle, that our attention will be especially directed.

The auricular complex of the artificially excited auricular contraction. The pace-maker of the heart.

Method.—In studying the electric changes produced in the heart as a result of its contraction in response to artificial excitation, it is very essential that the muscle should be damaged in the slightest possible degree, and it is necessary that when the curves are taken the heart should lie in the chest with its relationships to the chest wall undisturbed.

To produce artificial contractions, originating at definitely known points in the musculature of the auricle, necessitates the opening of the thorax, and the procedure adopted during the present experiments was as follows.

Dogs were rendered insensitive with morphia and paraldehyde, and a sufficiency of ether was employed to procure a complete or deep surgical anæsthesia. The thorax was opened by a flap method, either in the middle line or by making a window in the ribs, while the lungs were ventilated artificially. Small slits were made in the pericardium over the desired points, and insulated electrodes were attached to the auricle in definite regions. In the earlier experiments the electrodes were sewn into the epicardium, but in the majority of observations special electrodes terminating in minute trout hooks were employed. The fish hooks damage the musculature to the most trifling extent. In any given experiment no more than two, three, or four points of stimulation were chosen, and one of these invariably lay, as a control, at the junction of the superior vena cava with the auricle or in this neighbourhood. The remaining electrodes were attached to one or more of the following areas: the inferior vena cava, the pulmonary veins, the tips of the right or left auricular appendix, the base of the right

rhythm which is found when auricle and ventricle are completely dissociated). Two very different types of impulse formation are met with in the heart, a normal or physiological type, characterised by its long intervals of impulse formation, and a pathological type, characterised by the brevity of these intervals. The heart contractions, therefore, fall naturally into four categories:—

1. Contractions dependent upon a physiological type of impulse formation, and arising at the site of the pace-maker; the normal heart beat.
2. Contractions dependent upon a pathological type of impulse formation, and arising at the site of the pace-maker; the so-called "sinus extrasystole."
3. Contractions dependent upon a physiological type of impulse formation, and arising in an area of the musculature removed from the site of the pace-maker; for example, the "ideoventricular" contractions of the ventricle.
4. Contractions dependent upon a pathological type of impulse formation, and arising in areas of the musculature removed from the pace-maker; for example, the so-called "ventricular extrasystole."

appendix, or a point upon the internal surface of the right auricle. For the last-named observations a special electrode was devised. It consisted of a small glass tube carrying covered wires and having at its lower extremity two small exposed fish hooks in conduction with the wires. By employing this form of electrode certain points, subsequently ascertainable, could be reached, by way of the internal jugular vein and superior vena cava, upon the internal surface of the right auricle. In the successful experiments the electrodes were discovered attached to the mouths of the inferior vena cava and coronary sinus. With the electrodes in place the thorax was closed, all parts being brought into as natural a position as possible. All traces of air were removed from the pleural cavities and natural respiration was restored.

The electrocardiograms were obtained with Edelmann's large pattern of the string galvanometer of Einthoven ; the leads were from the right forepaw or right shoulder, and from the left hind-paw or groin. These leads were chosen because they presented a close parallel to those employed for routine clinical work.

The artificial contractions were excited by make or break induction shocks, usually signalled, and either single or successive. The successive excitations have been found to be the more convenient, but similar results are obtained by one or other method. In using regular and successive stimuli, an interrupter, of which the rate could be varied at will, has been employed, and a rate of rhythmic excitation, sufficient to outpace the normal heart rhythm* but insufficient to induce fibrillation, has been utilised. By these means a tachycardia may be excited from any chosen spot upon the auricular walls, with the heart beating under natural conditions, and the electric curve which such a rhythm gives rise to may be compared with that of the normal rhythm which reappears at the cessation of stimulation. The strength of stimulus chosen was the minimally efficient one, whereby the complication of the curves by the record of the stimulus discharge itself has been avoided in most instances. The desired restoration of natural breathing, and the need of obtaining a heart rhythm, not appreciably accelerated, prohibited vagal section.

The accompanying figures are examples of curves obtained by the methods described.

In previous communications, based in part upon clinical, in part upon experimental findings, I have repeatedly urged the recognition of the fundamental view that the electric curve is an important indication of the direction of the path pursued by the contraction wave in the musculature and that

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* I have employed very varying rates of stimulation in single animals, but in the accompanying curves give examples of artificial tachycardias only slightly faster than the normal rhythm. And I do so for these reasons; while the results obtained are the same, in so far as they affect my conclusions, with the faster rates the variation P tends to fall back upon the preceding T, and is consequently obscured. Furthermore, the comparison of normal and excited rhythms is the more exact, the more closely the rates of the respective rhythms correspond.

as a consequence it is an equally important guide to the birth-place of the impulse leading to such contraction. The conclusion that an abnormal auricular complex is significant in evidencing an abnormal or ectopic site of impulse generation is substantiated by the direct or experimental test.

The auricular complex which results upon excitation of an area in the neighbourhood of the junction of superior vena cava and right auricle.

In all, there are fourteen observations upon thirteen animals. The complete series of observations are shown in the opening columns of the accompanying figure (Fig. 1). This figure has been constructed by accurately tracing the complexes of the auricular representatives in the electric curves. The normal curves are given in the first vertical column (N), and the succeeding vertical columns include the curves obtained as a result of artificial excitations. The second column, with which we are at present concerned (S.V.C.), contains the complexes obtained upon stimulation of the superior cavo-auricular junction. Actual records are to be found in Figs. 4, 5, 6, 7, 13 and 15.

In all instances, stimulation of the superior cavo-auricular junction has yielded complexes bearing a striking resemblance to the normal complex. The duplication is usually absolute (Fig. 4 I), or almost absolute (Fig. 6 I). Where slight variation has occurred between normal complex and artificially excited complex, it has been, generally speaking, no greater than the variation met with in the outline of the normal complex in the same animal, as an accompaniment of respiration or some other and indeterminate cause*. But such variation is, as can be seen in the diagram, inappreciable in degree. The actual points of stimulation are shown in Fig. 2, an outline drawing of the base of the heart from which aorta and pulmonary artery have been removed. A single point has been utilised at the junction in all experiments

* A variation in the normal curve is shown in Fig. 5 III. The difficulty experienced in such instances is the choice of the complex for comparison with the artificially excited beat. Fortunately it is of rare occurrence. The accompanying figure illustrates the sole example met with during the present investigation

Fig. 1. A diagram showing the electric complexes of the auricular systoles in a series of thirteen experiments (natural size). The number of the experiment is indicated to the left. The point from which the auricular systole was propagated is indicated above. Each curve has been traced from the original photograph. Where slight variations in type have been present from beat to beat, that type has been chosen which is of most frequent occurrence. N = normal complex. S.V.C. = that obtained from superior vena caval areas (*h* the upper point, and *l* the lower point of excitation). I.V.C. = from inferior vena caval area, an asterisk is placed against curves obtained by internal stimulation. P.V. = from area of pulmonary veins. C.S. = from coronary sinus, internal stimulation. A.B. = from base of auricular appendix. R.A. = from right and L.A. = from left auricular appendix. The curves of the first six experiments were taken at a comparatively low speed, and the P-R intervals are therefore omitted. They are marked in seconds in the horizontal columns 7-13.

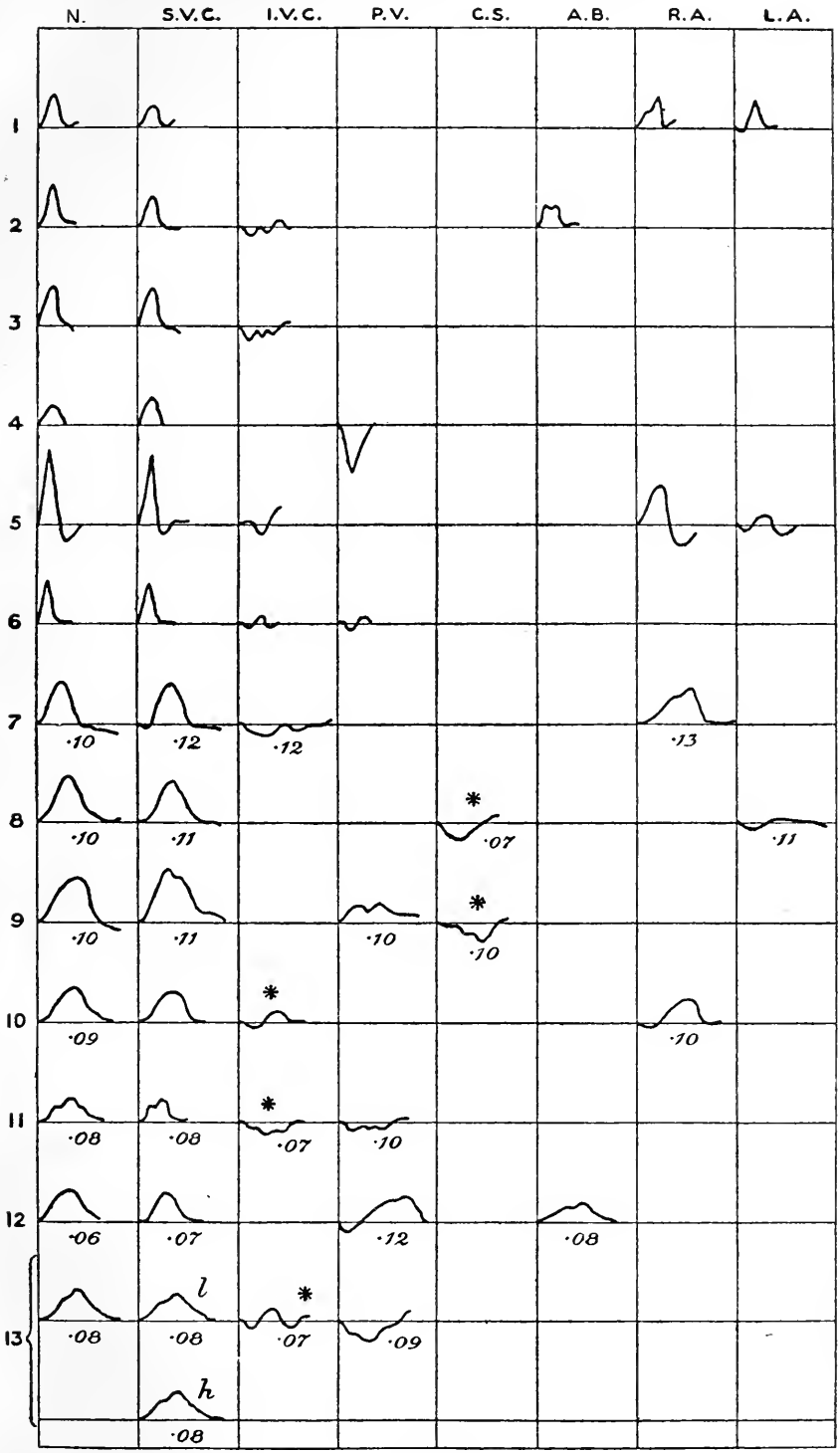
N.
S.V.C.
I.V.C.
P.V.
C.S.
A.B.
R.A.
L.A.
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Fig. 1.

but one (No. 13). In this instance two points were chosen upon the *sulcus terminalis* and a comparison between the two instituted*. The curves obtained are bracketed together in the diagram (Fig. 1).

It will be seen that the area from which artificially excited auricular complexes, similar to the normal, are obtainable, lies in and around the junction, and that a closer differentiation by means of the method employed is impracticable. Comparing normal and artificially excited curves, the differences noticed from animal to animal, where the excitation points are separated by $\frac{1}{2}$ to 1 cm., are very slight, and it cannot be said that any particular point on the junction line yields curves approximating most closely to the normal curve. The same statement applies to two separate points on the junction line, in one and the same animal.

The variations which are met with amongst the complexes obtained artificially from animal to animal from the junctional area are no greater than and are of similar character to the variations met with in the normal complexes of the same series.

The auricular complex which results upon excitation of an area in the neighbourhood of the inlet of the inferior vena cava.

There are eight observations in all.

We have seen that there is a variation in the complex yielded by excitation of the base of the superior vena cava, and that this runs hand in hand with the variations of the normal curves. Similar variations are met with in the curves resulting upon stimulation of the inferior vena cava (Fig. 1, column I.V.C., and Figs. 5 II and 15). The points of stimulation upon the superficies of the heart are shown in Fig. 3. They lie at the caudal and right portions of the base of this great vein, and largely over the termination of the coronary sinus. The excitation points upon the internal surface of the auricle are marked with an asterisk in Fig. 1. In experiment 11 the upper part of the vein, well inside the mouth, was the site of stimulation. In experiments 10 and 13 the upper or cephalic lip of the mouth of the vein. The mouth of the vein in the dog when viewed from within is very capacious. The attachment of the electrodes to its cephalic lip consequently places the point of stimulation much nearer to the superior vena cava than the points of stimulation upon the superficies (the points seen in Fig. 3).

In this series of curves there is very considerable variation in the type of complex shown, and no particular type can be regarded as specific. Nevertheless certain general statements may be made in regard to the curves.

* In giving diagrams of the points stimulated it is necessary to state that these points are approximately placed, and approximately only. The variation from animal to animal in the general conformation of the auricle has to be remembered, in particular the variation in the arrangement of the pulmonary veins. I have been guided in inserting them by the most fixed points, paying especial attention to the relationships to the S.V.C., the I.V.C., the *sulcus terminalis*, and the auriculo ventricular groove.

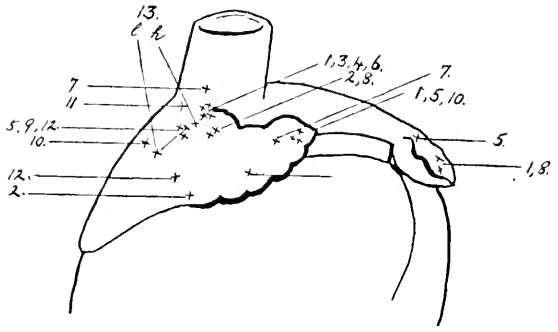

Fig. 2.

Fig. 2. An outline of the base of a dog's heart, to show the points of stimulation in the experiments. Seen from in front, with the aorta and pulmonary artery removed.

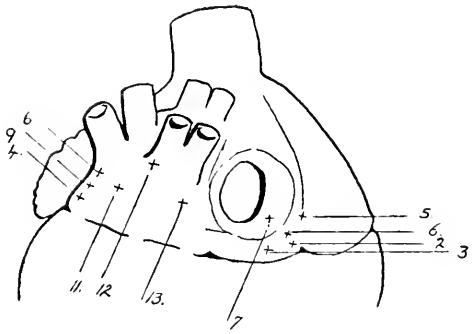

Fig. 3.

Fig. 3. An outline of the base of a dog's heart, to show the points of stimulation in the experiments. Seen from behind.

The complexes are always clearly distinguishable from the normal complexes. They are constituted by several distinct phases. As a rule there is an approximately equal distribution of upwardly directed (or base negative) and downwardly directed (apex negative) portions. The curves tend towards the isoelectric position. They commence with a downwardly directed (or apex negative) phase.

The auricular complex which results upon excitation of an area in the neighbourhood of the inlet of the pulmonary veins.

There are six observations (Fig. 1, column P.V., and Fig. 6 III).

The complex obtained from the neighbourhood of the pulmonary veins is more variable than that from the region of the inferior vena cava, the area is larger, and the general statements which may be made are therefore less numerous. The type of complex is always clearly distinguished from the normal complex. In five of the observations it commenced with a downwardly directed (or apex negative) phase. In one instance a very accentuated downward displacement was apparent (Fig. 1, experiment 4), and the point stimulated happened to be that which, in the series, was most removed from the S.V.C.. In another instance the complex was prominently in the upward direction (Fig. 1, experiment 12), and the point of stimulation was the most approximate to the S.V.C.. (The extent of upward or downwardly directed phases does not run exactly hand-in-hand with the distance from S.V.C.).

The auricular complex which results upon excitation of the mouth of the coronary sinus.

There are two observations (Fig. 1, column C.S., and Figs. 4 II and 6 II). The hooks of the internal electrode were found attached in each instance to the upper or cephalic lip of the coronary sinus. The curves are in the main downward displacements, and in one case there is a very appreciable shortening of the P-R interval as compared to the normal (Fig. 4). The shortening is from 0·10 to 0·07 sec.. This point of stimulation represents the nearest approach to the node of Tawara obtaining in the present series of experiments.

The auricular complex which results upon excitation of the base of the right auricular appendix.

There are two observations (Fig. 1, column A.B.).

The curves yielded are entirely base negative in direction, but less extensive than the normal curves, and are clearly distinguishable from

them. In type they approach more nearly to those obtained from the superior cavo-auricular area than do any of the curves hitherto considered.

The complex resulting upon excitation of the tip of the right appendix.

There are four observations (Fig. 1, column R.A., and Fig. 5 I).

The curves are not dissimiliar to those obtained from the superior cavo-auricular junction, but never duplicate them. The base-negative amplitude is less extensive, the rise is less abrupt, and there is a tendency towards the appearance of a distinct notch on the upstroke.

The complex obtained upon excitation of the left appendix.

There are three observations (Fig. 1, column L.A., and Fig. 4 III). The curves vary considerably. They are always quite dissimilar to the normal complexes. They have commenced with a brief or prolonged downward (apex negative) displacement.

General findings.

The observations, from a description of which we now proceed, permit us to formulate certain general statements.

A contraction of the auricle, excited artificially in the neighbourhood of the base or inlet of the superior vena cava, invariably yields an auricular electric complex identical with or closely resembling the auricular complex of the normal heart beat. No other area of the auricular musculature, when stimulated, propagates a contraction which yields an electric curve of the same type, but it is noteworthy that in its general conformity the complex considered approaches the normal type most nearly according as the point excited approaches the superior vena cava. The deduction is clear, while it is believed that, *cæteris paribus*, the electric curve is distinctive of the course pursued by the contraction wave, and, therefore, that it indicates the point at which such wave of contraction starts. We have curves propagated from a large series of points under review, and of these a certain number show a distinctive feature, namely a close resemblance to the natural curves obtained from the same animals. The shape of the auricular complex accompanying heart beats artificially provoked and starting in the area of the superior cavo-auricular junction, provides convincing evidence of the proximity of this junction and the pace-maker of the heart. A more accurate localisation by the means employed isimpracticable as we have seen, but the

observations narrow the field of enquiry to a comparatively small area in the immediate neighbourhood of Keith and Flack's node*.

The second general conclusion of importance which may be drawn from the experiments concerns the identification of spontaneous beats arising in areas of the auricular musculature removed from the pace-maker. For, both in experiment and in clinical cases, spontaneous auricular systoles are not infrequently observed, which are represented in the electric curves by outlines distinct from the outlines of the normal beats. In such instances it may be asserted that such beats have arisen ectopically. Furthermore, the more prominent the upwardly directed (or base negative) phases of such ectopic curves, and the closer the resemblance borne to the normal type, the nearer is the extraneous point of impulse formation to the pace-maker. A curve which commences with a downwardly directed (apex negative) phase and is continued in an upward (or base negative) direction arises in all probability from the central zone of auricular tissue (for example, from the regions of the mouths of the inferior vena cava and pulmonary veins). A curve composed of phases falling entirely in the downward direction may similarly be attributed to the lower zones of the musculature (for example, the lowest part of the septum, where lie the mouth of the coronary sinus and the node of Tawara)†.

The auricular complex of the abnormal auricular contractions as they are met with in clinical cases.

The observations have been made upon patients in whom single premature beats, or successive beats of a similar nature (paroxysms of tachycardia) have been frequent. In each case the relative positions of the auricular and ventricular contractions in the abnormal heart cycles have been fully confirmed by means of polygraph records. From a number of such patients, a few cases are chosen for purposes of illustration and the clinical histories and conditions of these have been already published.

Where an otherwise regular rhythm is disturbed by premature or by successive and abnormal beats arising in the auricle, the auricular complex presents definite characteristics. In the majority of patients it can be

* Another galvanometric method of localising the pace-maker may be employed. By leading off from the auricle itself, it may be ascertained which point of its musculature first demonstrates negativity, for negativity represents activity. Some preliminary observations have been undertaken from this point of view, and have been referred to in another place. It was found in two experiments that the neighbourhood of the superior vena cava first becomes negative during the progress of the electric changes accompanying the auricular systole. But at this stage of the observations I heard through Dr. Koch of Dr. Wybauw's observations, and understanding from Dr. Wybauw himself that they were arriving at completion, this line of investigation was not pursued.

† A curve, completely apex negative in direction, has also been obtained from the inferior cava, and from the neighbourhood of the pulmonary veins at a point far removed from the S.V.C..

shown that the complex of the abnormal beats is constant in the same patient from beat to beat or from day to day and month to month. The focus of disturbance in the auricular musculature is, therefore, a restricted one. In only one definite instance have beats been observed, which arose in several auricular foci. (Electrocardiograms from this case are shown in Figs. 9 and 11; the case is also the basis of a separate communication by Dr. Marris.)

From case to case the auricular complexes show marked variation. Reference may be made to the figures which are described in the ensuing paragraphs.

a). In Fig. 8 a short strip of electrocardiographic and radial curve is shown, from a patient, the full details of whose case have been recorded in the last number of this *Journal*. Two premature beats arising in the auricle are present. In each instance the premature auricular contraction coincides with the preceding ventricular systole, and a large variation consisting of the superimposed P and T variations results. I have many curves from the same case and in some of these P falls a little later in relationship to T; the component parts of the composite variation are more clearly differentiated in these instances. In the illustration given it will be found that the height of the normal P variations when added to corresponding T variations yields a sum which is equivalent to the height of the composite variation.

The peaks of P and T have fallen precisely together. We have to deal, therefore, with an auricular complex, in the instance of the premature beat, which is of equal height with the normal P variation of which the displacement is entirely upward in direction*.

b). Fig. 9 is an example of simultaneous electric and radial curves from a case of paroxysmal tachycardia, described in the last number of this *Journal*. The paroxysms were shown to have their origin in the auricle and it was considered probable that they arose from the lowest level of the musculature. It will be observed that accompanying the early beats of the figure the P variations are normal in form. During the paroxysmal stage the P variations are inverted and entirely downward (or apex negative) in direction. The P-R intervals are also shortened during the paroxysmal stage. The nearest approach to this type of complex, given by the experimental observations described in this paper, is that shown as proceeding from the coronary sinus in Fig. 4 II.

c). In an earlier paper a case of paroxysmal tachycardia was described and it was shown that the paroxysms themselves and the premature beats disturbing the slow periods were auricular in origin. A new figure is published from this case (Fig. 10). In this figure a single premature beat is shown in each of the separate tracings. In every instance the premature P variation falls with the preceding T variation and deforms it. As in Fig. 8 the two variations, the abnormal P and the abnormal T, are algebraically superimposed. The composite curve may be resolved by subtracting the

* This figure shows a distinct prolongation of the premature P-R interval.

normal T. It is obvious that the type of abnormal P variation consists of a small variation in the downward direction, but that in the main it is isoelectric, for the T upon which it falls is notched in its opening phase. Fig. 12 is a curve from this case in which with the occurrence of a paroxysm of abnormal beats each alternate auricular impulse is blocked on its way to the ventricle. As a result the alternate P variations fall clear of the preceding ventricular complexes and the shape is clearly shown*. A small downwardly directed peak is succeeded by a long isoelectric period.

d). An example of a purely isoelectric P is shown in Fig. 11, and was obtained from the same case as the curve shown in Fig. 9.

The premature beats are known to be auricular in origin, for no other form of interruption of the normal rhythm has been evidenced by venous curves taken from this case, and also because all such beats show an absence of a complete compensatory pause. A purely isoelectric representative of the auricular systole has not occurred in the experimental observations.

The examples which have been given (*a*, *b*, *c*, and *d*) should suffice to illustrate the three main types of auricular electric variation as they are met with in clinical studies. They group themselves as follows :—

a). A full base negative variation.

b). A full apex negative variation with or without shortening of the P-R interval.

c and *d*). An auricular representative which is isoelectric (*d*), or which tends towards this position, with a bias somewhat towards the base or towards the apex negative condition (*c*).

They are recognised as significant of premature beats arising :—

a). In the upper regions of the auricle; that is to say, in the neighbourhood of the pace-maker.

b). In the lowest region of the auricular musculature; that is to say, in the neighbourhood of the node of Tawara; or where there is no shortening of the P-R interval, possibly from the region of the pulmonary veins.

c and *d*). In the middle region of the auricle; that is to say, in the neighbourhood of the inferior cava or pulmonary veins, or left appendix, with a bias towards the superior vena cava on the one hand or the lower levels of the auricle on the other hand.

An absolute localisation is of necessity impossible at the present stage of the enquiry; nevertheless localisation is obviously possible within certain limits.

* Periods of this mechanism were graphically recorded by means of the polygraph, and were published in an earlier paper. They were interpreted as periods of "interpolated auricular extrasystoles." In the light of the electric curves this explanation can no longer be held.

On the other hand the most important conclusion to which the attempt at localisation leads is of a perfectly precise nature. It is a conclusion which has been previously arrived at from theoretical considerations and other data. We know positively that not only single *ectopic* beats but that successive ectopic beats, constituting a rhythm, are to be found, and not uncommonly, in clinical cases. The comparison of clinical and experimental curves proves beyond question the generation of certain paroxysms of tachycardia in areas of the auricular musculature removed from the pacemaker. These cases are illustrations of a temporary dislocation of the rhythm of the heart from the normal pace-making area at the base of the superior vena cava, to points in the remaining auricular musculature.

THE VENTRICULAR COMPLEX ACCOMPANYING THE RESPONSE TO THE ARTIFICIALLY EXCITED AURICULAR CONTRACTION AND ACCOMPANYING THE RESPONSE TO THE ABNORMAL AURICULAR CONTRACTIONS AS THEY ARE MET WITH IN CLINICAL CASES.

When an impulse starting a ventricular contraction originates in the supraventricular portions of the heart, we have reason to believe that the contraction of the ventricle is started in those portions of the ventricular walls which are most directly united to the auricular musculature. We should be led to anticipate that all such ventricular contractions would yield a specific and normal type of ventricular complex. Within certain limits this rule holds good (Fig. 8). But at the same time there are numerous exceptions to it and the conditions giving rise to them require closer examination. I do not propose to give a full account of the changes or combination of changes encountered in the ventricular complex, but choose those varieties which stand out most conspicuously.

The commonest type of ventricular complex following an artificially excited auricular contraction in experiment, and the most frequent type in clinical cases where a normal heart rhythm is interrupted by premature or paroxysmal beats of auricular origin, is of the normal form and consists of R and T (or R, S and T or Q, R, S and T) variations, which approximately duplicate the normal ventricular complex (see Figs. 4 and 8). In such curves the peak R usually tends to diminish in size according to the degree of prematurity of the contraction which originates it.

1). A notable change is seen in certain experimental instances. Clinically I have not as yet met with it. It consists in changes *chiefly* confined to an alteration in the extent or direction of the phase T, and is illustrated in Figs. 13 and 14. The normal complexes of these figures are characterised by well-marked and upright R and T phases and a small variation S. The premature beats, two of which appear in Fig. 13, and one of which appears in Fig. 14, show clearly marked differences. Accompanying the earliest

beats the T variation is completely inverted (the first premature beat of Fig. 13). Beats which are not quite so premature show both an upwardly and a downwardly directed peak (the premature beat of Fig. 14). While still later abnormal beats show a simple decrease in the amplitude of T (the second premature beat of Fig. 13). The phenomenon is extended to the beats which succeed the premature beats, for in these the amplitude of T is exaggerated. These changes may occur with or without an associated change in the amplitude of R.

2). The second change of importance which is met with is a notable alteration in the amplitude of R, but the alteration referred to is usually accompanied by an inversion of or increase in the depth of T (the latter is present, where T is originally inverted). At the same time the depression S disappears. In Fig. 13 there is a very slight but definite increase in the amplitude of the R (of the first premature beat), and the phase S, which though small in the normal beats is quite distinct, is absent in the premature complex. More pronounced instances of this phenomenon are shown in Fig. 7. In Fig. 7 II and III single artificially excited beats are shown. There is one in Fig. 7 III and there are two in Fig. 7 II. If the three beats are compared it will be seen that where the excitation falls late in diastole the resultant ventricular complex is a duplicate of the normal (Fig. 7 III), while, as it falls earlier and earlier in the diastole of the preceding heart cycle, R rapidly increases in amplitude and T tends to become more depressed. In this animal the T of the normal beat was inverted, but the same changes are frequently seen where T is originally upright; in such instances T may become inverted. In experimental auricular tachycardias precisely similar changes are noticed, and they vary in degree, according to the rate of the rhythm provoked. This is clearly shown in Fig. 7 I. As an accompaniment of the faster tachycardia, the amplitude of R is greater, and T is slightly more depressed (compare Fig. 6 III, from the same animal).

Similar events are seen in clinical cases. It is usual to find that the peaks R of auricular tachycardias are taller than those of the normal beats in the same patient. Single premature beats, showing parallel changes, are also met with clinically. An example is shown in Fig. 11. Two ectopic beats are depicted which have arisen in the auricle. The representative of the auricular systole is absent, the auricular curve is in fact isoelectric. The peaks R are greatly exaggerated and T is in each case inverted. The importance of the recognition of this type of change in the ventricular complex of premature or successive abnormal beats springing from the auricle, lies in the resemblance of the type to the complex accompanying an ectopic beat arising from the musculature of the basal and right portions of the ventricle.

I have described two varieties of change (1 and 2), in one of which with the early abnormal beat the *chief* alteration is in the form of a depression or inversion of T, in the other of which the *chief* alteration is an increased amplitude of R. But it should be clearly understood that while the two

phenomena are certainly largely independent of each other, yet they are usually found together, one or other predominating.

3). Another important change seems to stand by itself. It is illustrated in Figs. 10 and 15, and is perhaps the most remarkable of all. It has been met with in three experimental cases and in two clinical cases.

In Fig. 15 are four curves, A, B, C, and D, from a single animal. The point of excitation in A and C was the superior vena cava ; and in B and D the inferior vena cava. The differences in the premature P variations according to the site of stimulation are characteristic. Now in A and B excitation fell at an early stage in the diastole, while in C and D it fell later. The change in the ventricular complex which is shown in A and B has never been encountered except when the interval between premature beat and the preceding heart contraction has been short, and the type tends to exaggerate as the interval is shorter. The chief change is a striking increase in the amplitude of S and an increase in the prominence of T. In each of the three experiments the same facts were observed. The increase of S is not associated with its original prominence in the normal beat, for in the remaining animals S was small in the normal complexes. But an examination of all the curves shows that its great amplitude in the figured instance is in part attributable to its original prominence. It is entirely independent of the site of stimulation, for it has been produced from the inferior and superior vena cava (Fig. 15 A and B) and also from the pulmonary veins. (The independence of the changes, recorded in previous paragraphs, of the site of stimulation is equally true.)

A point to which attention is specially directed, and which will be discussed at a later stage, is the increase of the P-R interval accompanying the premature beats in this figure.

In a previous communication three types of ventricular complex accompanying premature auricular beats were described in curves taken from a single patient.

For convenience of description they were designated types I, II, and III. Our attention will be confined for the present to the types I and III, for of type II there is neither an experimental duplicate nor is there further evidence in regard to it.

In Fig. 10 five strips of curve are given, and they were taken, from the patient referred to, at one sitting. Each includes a single ectopic beat. Following the onset of the second rhythmic ventricular complex in each curve at a time distance of 0·2 sec. is the representative of the ectopic auricular contraction. It manifests itself, as previously noticed, by notching the preceding T in the downward direction. This P variation is followed in each instance by a ventricular complex, and in 10 A it conforms to what I originally designated type I, while in Fig. 10 E it is of the form of type III. The remaining curves are arranged in their natural order. The P-R intervals of the several abnormal beats decrease as they are traced from above

downwards, namely, from 0·26 to 0·14 sec..* The parallel to the experimental curves shown in Fig. 14 is remarkable, and the underlying mechanism is probably of a similar nature. The ventricular contraction which is early has the S phase exaggerated, and in one example, Fig. 10 D, T is also exaggerated. The transition of the types in Fig. 10 is not perfect, for while S increases progressively, the amplitude of R decreases only as far as Fig. 10 D, and in 10 E shows an increase of its excursion.

It is noteworthy that in the clinical instance there are marked changes in the conduction intervals, and these in themselves account for the varying length of pause existing between premature ventricular beat and its predecessor. Changes in conduction were also described in connection with Fig. 14, but there is this difference; although the earlier ventricular beat in both clinical and experimental instance is accompanied by the exaggerated S phase, yet the P-R interval in the clinical instance is shorter when the abnormal beat is earliest and the reverse is the case in the experimental example.

The observations upon the changes in the conduction intervals lead up to the final remarks which I propose to offer upon the variations obtaining in the ventricular complexes accompanying abnormal contractions arising in the auricle, for I shall content myself at the present time by placing the main facts on record. At the same time I desire to advance a view as to the causation of these and other variations, but do so in the most tentative fashion. The argument centres around the following facts. The chief changes are met with in the earliest of the premature beats, and such beats are frequently accompanied by evidences of deficient conduction in the musculature. In studying the ventricular complexes of beats arising ectopically in the ventricle itself, I have been impressed by the absence or relative absence of change in the conformity of the curves according to the instant in diastole at which they occur or are excited. In this respect they offer a marked contrast to the ventricular complexes of ectopic beats arising in the auricle. Now when the ventricle is excited by the application of a small stimulating electrode to its walls, the contraction is propagated *from a single point*, while in the case of a ventricular beat originating in a supra-ventricular impulse, the impulse is received on right and left side and the contraction is initiated in at least two areas, the arborisations of the right and left branches of the bundle. The suggestion offered is one which is parallel to that put forward by Einthoven in explanation of the variations which occur in the normal electrocardiogram from man to man or animal to animal. The distribution of the impulse awakening the ventricular response may vary. It is possible that the variations in the ventricular complex associated with a premature auricular contraction are similarly

* In the original account I stated that the differences in the type of ventricular complex could not be accounted for by differences in time relationships. When the paper was written I had but few examples of type I, and sufficient observations could not be made upon it. The statement applied more particularly to types II and III. The origin o ftype II is still as obscure as before.

dependent upon a variation in the impulse distribution from beat to beat. The view is supported by the observation that certain of the most highly atypical complexes are frequently accompanied by obvious changes in the conduction intervals.

Supposing that such changes are located in the junctional tissues, the A-V bundle and its arborisation, may it not be that there is a greater defect in one part of the system than in another and that the defect may vary quantitatively from time to time, and that as a consequence the impulse descending from the auricle first reaches one part of the musculature of the ventricle when the contraction is early, and another portion of the musculature when the contraction is later? A complex of the type shown in Fig. 11, and one which resembles that obtained on provoking a contraction from the basal and right portions of the ventricle, would receive explanation along these lines by supposing that at the time of the propagation of the impulse to the ventricle the function of the right branch of the bundle was further restored than that of the left branch. The impulse under these circumstances would travel more rapidly to the right ventricle, and awakening a response in it, the whole ventricle (right and left) might be thrown into contraction as a result of the distribution of the impulse to this area alone. If such were the conditions, a ventricular complex, simulating that obtained on artificial excitation of the basal and right portion of the ventricle, would certainly be anticipated.

Conclusions.

1. The form of the auricular electric complex accompanying an auricular contraction is intimately connected with the focus in which such a contraction is generated.

2. No two areas of the auricular musculature give rise to contractions represented by similar complexes. The areas from which distinct complexes are obtainable are relatively small.

3. The auricular complex of an excited auricular contraction may be normal in form, diminished, or partially or completely inverted. The auricular tissue may be arbitrarily divided into three zones, an upper, a lower, and a central. The upper zone will yield complexes of a chiefly upright form, the lower zone those of a chiefly inverted form, while the central zone will yield curves which approach to an isoelectric state.

4. The normal auricular complex is most closely simulated by beats excited from the neighbourhood of Keith and Flack's node. The pacemaker of the heart is therefore situated in the neighbourhood of the superior cavo-auricular junction.

5. The ventricular complex accompanying premature beats arising in the auricle is subject to considerable variation. The variations are independent of the site of impulse production in the auricle, but are largely though not entirely dependent upon the instant at which the ventricle contracts in relationship to the preceding systole.

6. Experimental premature contractions and tachycardias provoked in the auricle show many features in common with premature auricular contractions and spontaneous tachycardias as they are met with clinically. The points of origin of the abnormal clinical contractions may be localised within certain limits.

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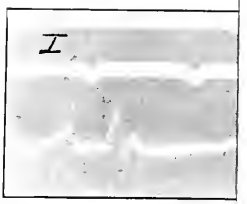
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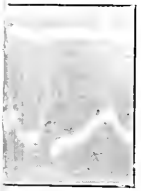

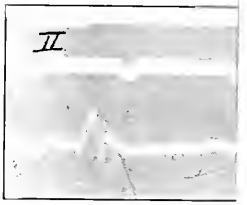
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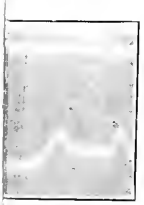

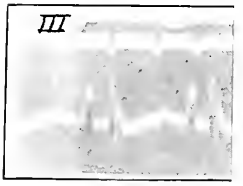
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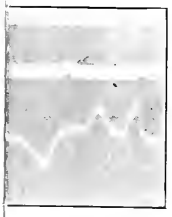


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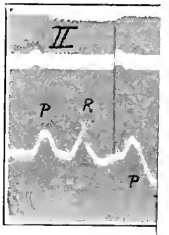
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Fig. 4, I, II, and III. $\frac{1}{2}$ linear. Dog 8. In each strip of this and the three succeeding figures the termination of a long continued tachycardia is shown. In each curve portions of three beats, artificially excited from a known point of the auriculo-auricular musculature by means of regular induction shocks, and portions of three beats of the normal rhythm, are shown. The stimulus is signalled in the top line, the time marked in 0.2 sec. is shown in the second line, the electrocardiogram in the third. The sites of stimulation were, I, the superior cavo-auricular junction; II, the mouth of the coronary sinus, internally; and III, the left appendix.

Fig. 5, I, II, and III. $\frac{1}{2}$ linear. Dog 7. Similar curves to those of Fig. 4, but excited from, I, the right auricular appendix; II, the inferior vena caval area; and III, the superior vena caval area. III is at a slower speed, for the purpose of showing the variation in the form of the normal P peak which may be encountered. So marked a variation is very infrequent.

Fig. 6, I, II, and III. $\frac{1}{2}$ linear. Dog 9. Similar curves to those shown in the preceding figures. The points of stimulation were, I, the superior vena caval area; II, the mouth of the coronary sinus, internal surface; and III, the pulmonary vein area.

Fig. 7. $\frac{1}{2}$ linear. Dog 9. I, A similar curve to those shown in preceding figures; a tachycardia of greater rate has been excited from the area of the pulmonary veins. In this figure the make and break excitations effect the electric curve; II, single interruptions of the normal rhythm. Two abnormal beats are shown. The stimulus was applied to the superior vena caval area. III, a single premature beat, occurring late in diastole, and excited from the superior caval area, is present.

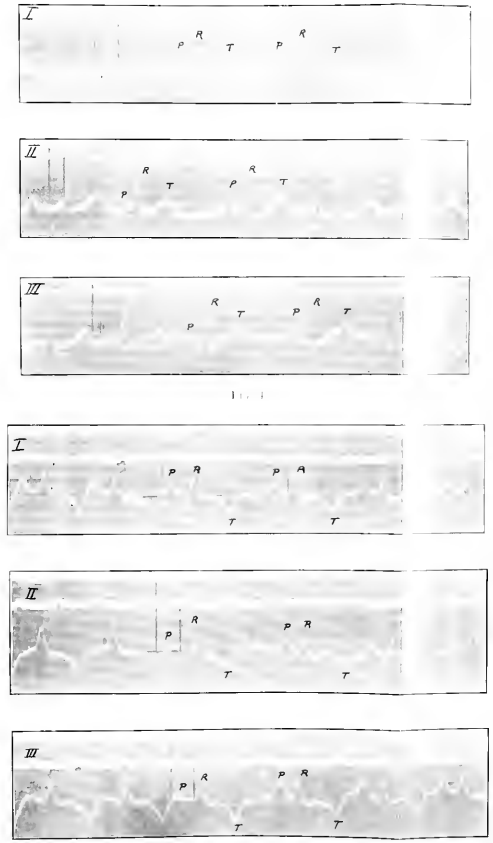


Fig. 6

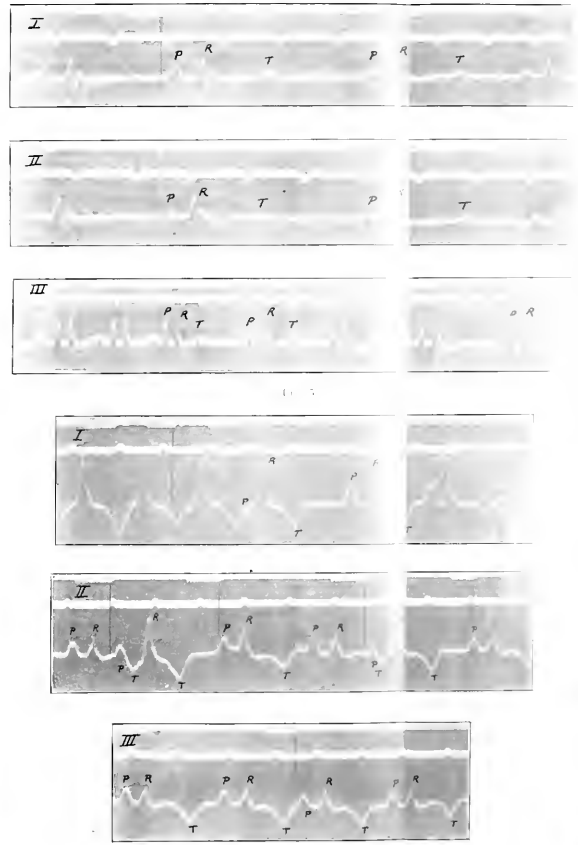
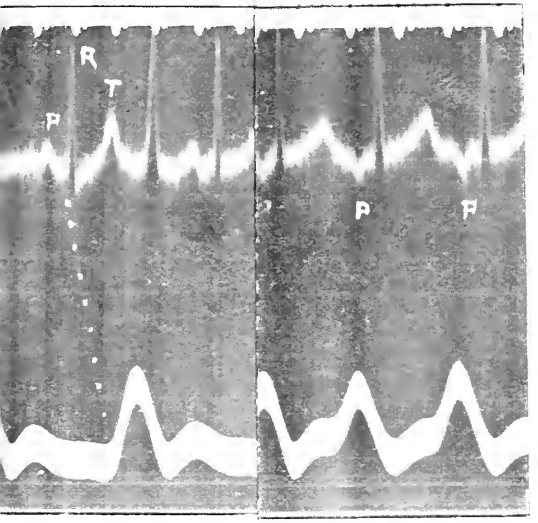
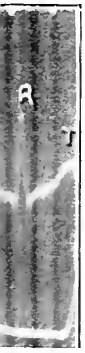


Fig. 7





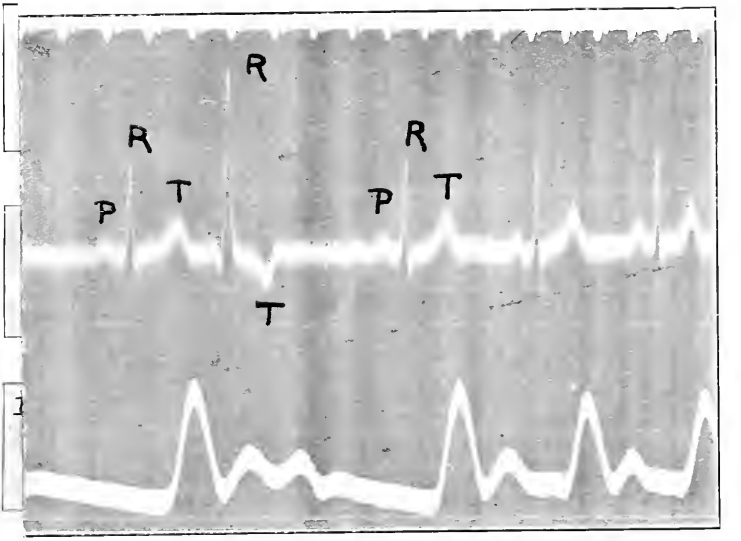


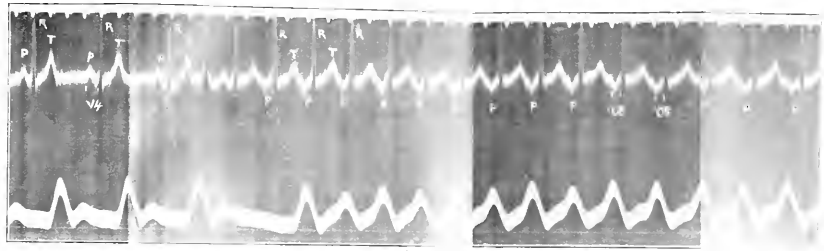
Fig. 11.

Fig. [illegible] Electrocardiogram of a patient affected by mutual stimulation of ventricular heart contractions arising in the upper zone of the auricular musculature.

Fig. 9. Electrocardiogram from a case of paroxysmal tachycardia. Showing a paroxysm of ectopic beats arising in the lowest zone of the auricular musculature.

Fig. 10. ½ linear. Five curves from a patient exhibiting paroxysmal tachycardia. The curves were taken at one sitting, and while the pulse was slow. Each strip presents a single ectopic contraction, arising in the central zone of the auricular musculature. They are [illegible] the transition from one type of ventricular complex to another, and illustrate the interval as marked in decimals of 0·2 sec.

[illegible] the same case as that from which Fig. 9 was obtained. Showing two ectopic beats. The [illegible] the representative is isoelectric, the ventricular complex [illegible] The [illegible] contractions probably arose from the central zone of the [illegible]



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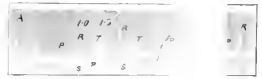

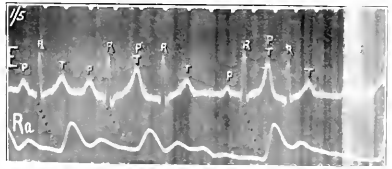

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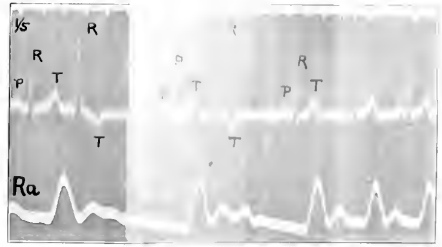

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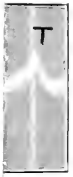

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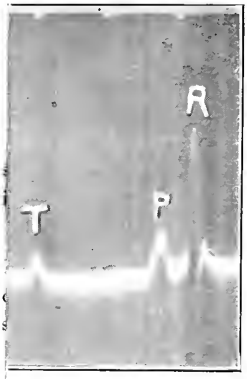

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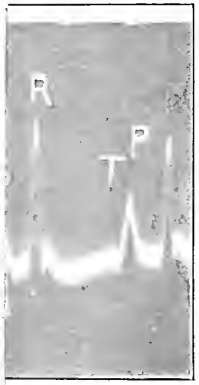

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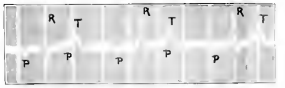


Fig. 12

Fig. 12. — Ibidem. From the same case as that from which Fig. 10 was obtained. A short strip of curve is given from a paroxysm arising in the auricle. Each alternate auricular impulse is blocked.

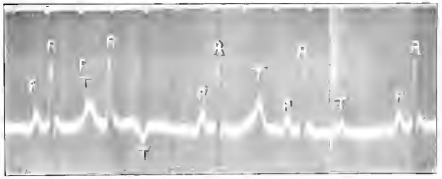


Fig. 13

Fig. 13. — Dog I. An experimental curve showing two premature beats excited from the superior vena cava. The premature and so-called "post extrasystolic" ventricular complexes show marked changes in the ventricular.

Fig. 14. — Dog I. A premature beat excited from the left appendix.

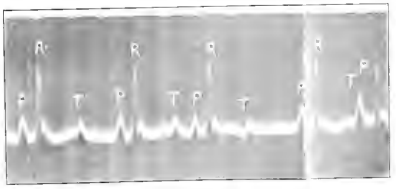
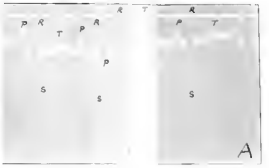
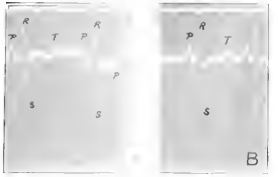
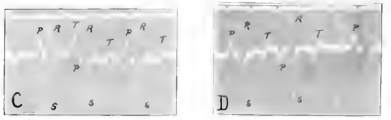


Fig. 15

Fig. 15. — Dog I. Four experimental curves. Each shows a premature auricular contraction. A and C were excited from the superior, B and D from the inferior caval area. A and B were early, and D late, in diastole. To show a special type of ventricular complex and to compare with Fig. 10 I.







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AURICULO-VENTRICULAR HEART-BLOCK AS A RESULT OF ASPHYXIA.*

By THOMAS LEWIS and G. C. MATHISON.

(*From University College Hospital Medical School.*)

In an article upon the mammalian spinal animal, recently published, Sherrington[2] speaks of a sudden diminution of heart rate in asphyxia. He writes as follows: "From a frequency of 300 per minute it now absolutely abruptly drops to 140 to 150 per minute," and again, he says, "This sudden check of the heart's rate is not due to vagus action, for it occurs still quite typically after administration of atropin has set aside all cardiac inhibition obtainable by stimulation of the vagus trunk in the neck."

This year Roaf and Sherrington[1], writing upon the same subject, state that "At a certain stage of asphyxia there ensues, as shown in the previous paper, an abrupt reduction in the frequency of the ventricular beat, not due to vagus inhibition. It is in fact due to heart-block."

In view of the fact that neither Sherrington nor Roaf and Sherrington have brought forward evidence of the occurrence of heart-block during asphyxia, and knowing that an apparent halving of ventricular rate may occur in the mammalian heart, in the absence of heart-block, and in the absence of vagal inhibition, we considered it advisable to investigate the matter more closely. Using Edelmann's large pattern of Einthoven's string galvanometer, we have taken electrocardiograms from the right fore limb and left hind limb of cats.

The heart contractions have been recorded in the decapitated or spinal cat, and in the decerebrate animal under artificial respiration. They have also been recorded in the intact and curarised animal, with the vagi intact and with the vagi divided. Further, they have been registered in the spinal animal under doses of atropine, sufficient to paralyse the vagus terminations, as tested by faradisation of this nerve in the neck. Our results, in so far as they are stated in this paper, have been uniform.

It was desirable that the records should be taken at a moderately fast rate for purposes of measurement, and as a continuous record of a complete asphyxial observation, from its start to its finish, was impossible at such speeds, we took sample tracings at intervals of about 30 sec.. These intervals, as stated in the accompanying table, are sometimes shorter and sometimes longer than 30 sec., for in watching the movements of the shadow

*An account of observations undertaken under the tenure of Beit Memorial Fellowships.

of the string, it is not difficult to appreciate certain changes in the mechanism of the heart-beat, and often with the onset of such a change we obtained an early or late tracing. The first table which is given is a fairly characteristic example of such an observation. It differs from the remaining experiments in the fact that the onset of heart-block is, as a rule, earlier than is here shown.

TABLE I. Cat I. Obs. 4. Decapitated Cat. Artificial Ventilation. 1/100 gr. atropine sulphate.

Duration of Asphyxia in min. & sec.	Auricular Rate.	P-R. Interval.	Ventricular Rate.	REMARKS.
0,0	124	·08	124	
0,30	125	·08—·09	125	
1,0	127	·07—·08	127	
2,0	127	·08	127	
2,15	127	·08	127	
2,30	161	·08—·10	161	
3,15	180	·08	180	
3,30	182	·08	182	Sl. variation of auricular rate.
4,0	161	·08	161	
4,15	142	·12—·13	142	Prolongation of P-R interval.
5,0	122	·12—·13	122	Sl. variation of auricular rate.
5,30	113	·12—·13	113	
5,45	107	·12—·13	107	
6,0	97	·14—·16	48·5	2 : 1 H.B., Sl. variation of auricular rate.
6,30	96	·16	48	
7,30	90	—	52	C. H. B.

With restoration of ventilation the heart rate quickened to the original rate, and the heart-block disappeared.

TABLE II. Cat 10. Obs. 4 Intact animal; artificial respiration; urethane and curare; vagi cut.

Duration of Asphyxia.	Auricular Rate.	P-R. Interval.	Ventricular Rate.	REMARKS.
0,0	192	·10	192	
1,0	192	·10	192	
1,15	187	·10+	187	
1,30	187	·10	187	
1,45	205	·10	205	T increasing
1,50	205	·12	205	T markedly exaggerated
2,30	150	·13	150	
3,0	130	·14—·15	130	
3,5	126	·15—·16	63	2 : 1 H.B.
4,15	105	—	67	C.H.B. One extrasystole.
4,40	101	—	59	C.H.B.
5,10	98	·18	49	2 : 1.
5,45	—	—	33	Auricle not recording.

The heart subsequently showed complete recovery, the P-R interval measuring ·08—·10 sec (cf. Fig. 4c.).

From left to right it indicates the duration of asphyxia, the rate of the auricle per minute, the P-R intervals in seconds, and the ventricular rate.

The second table is similarly arranged ; the time relationships are more typical. It shows an exceptional occurrence, the break back of complete to 2 : 1 heart-block.*

Within two or three minutes of the onset of asphyxia the rate of the auricles and consequently that of the ventricles increases. At $1\frac{1}{2}$ to $4\frac{1}{4}$ minutes (usually early) a prolongation of the P-R interval occurs, and this is the first evidence of the subsequent fully developed heart-block. It is either accompanied or directly preceded by a retardation of the auricular rate, and the decrease may be considerable. Following upon this stage is a further and steady decrease of auricular rate, and it is associated with the appearance of other grades of heart-block, of which examples are published (Fig. 1). The prolongation of the P-R interval becomes exaggerated, and it may lengthen to double or treble the original measurement (the longest interval recorded has been 0·3 sec.). (The normal interval for cats is about 0·08 to 0·1 sec.). Within two minutes (usually less) of this evidence of diminished conductivity of impulse transmission from auricle to ventricle, auricular impulses fail to reach the ventricle. At first there may be an occasional dropped beat (Figs. 2 and 3), there may be dropped alternate beats (2 : 1 heart-block, Fig. 1 III). Where single beats are dropped a condition comparable to that which is found in clinical cases has been met with. The already lengthened P-R interval rapidly increases still further up to the point where the dropped beat is seen. This preliminary lengthening of the P-R interval is clearly shown in Figs. 2 and 3 and the intervals increase to such an extent that the auricular systoles (P) fall back upon the preceding ventricular systoles (R and T), so that the contraction is partially synchronous in the two chambers. The first P-R interval succeeding the failure of a ventricular response is invariably relatively short, a shortening which has been frequently pointed out in clinical cases and which is attributable to the long rest which precedes it.

Following upon the stage of prolonged P-R interval or upon a period of dropped beats, 2 : 1 heart-block manifests itself (Fig. 1 III). The auricular rate during this period is always markedly retarded (despite the section of the vagi, or the administration of atropine), and the P-R intervals retain their increased length. They may be shorter, or of the same length or even slightly longer than the longest P-R intervals of the preceding phase. They are usually long as in Fig. 1. The duration of the 2 : 1 block is variable, but generally continues for a minute or two. It is succeeded by a period of complete heart-block, in which the auricular rate is approximately twice that of the ventricle, but in which there is no simple arithmetical ratio between the rhythms of the two chambers. There is complete dissociation, and the auricular variations (P) fall at varying times in relationship to the ventricular

* This reappearance of 2 : 1 heart-block does not necessarily indicate a decrease of impairment of conductivity. It may be explained as a result of the slowing of an ideoventricular rhythm.

representatives (R and T). Frequently the representatives of auricle and ventricle coincide, a phenomenon well shown in Fig. 1 IV. The first P of this figure falls in the centre of the ventricular systole, the second in the middle of diastole, while the third coincides with and raises the apex of the variation T of the second ventricular systole. An auricular variation is known to have occurred at this instant, for the superimposition (comparing the T variations of the two ventricular cycles) is exact, and a P variation is expected at this point. We have a number of curves of complete heart-block produced in this way, but not so many examples as we have of the preliminary stages, for the condition of the animal becomes critical, and often re-establishment of respiration and recovery is desired. Nevertheless, recovery and absolute recovery of the conductive functions may occur subsequent to the period of complete dissociation, an event which we have thrice witnessed, and which is exemplified in Fig. 4 *c*.

The recovery from complete heart-block is relatively slow, and is pursued through similar stages to those of its production, though the order is reversed. Recovery from 2 : 1 heart-block is faster. There is a short latent interval of about 10 to 20 sec., and then within a few heart cycles the condition 2 : 1 heart-block passes to one of complete restoration ; that is to say, the P-R interval returns to its original length at the commencement of the observation (Fig. 4 *a* and *b*). The change is the more remarkable for its suddenness, in view of the acceleration of auricular rate which accompanies it (Fig. 4 *a* and *b*). Recovery is permanent when it is complete.

During the course of the experiments we have noted many other phenomena of interest, but these, being still obscure, we reserve—two further observations alone require description at the present time.

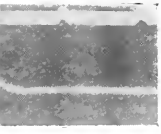
1). At or about the time when the heart appears to waver between a condition of 2 : 1 heart-block and regular sequential contraction accompanied by prolongation of the P-R interval, it not infrequently happens that passing into the latter state it exhibits a regular alternation of the P-R intervals. This in turn gives rise to a slight grade of ventricular bigeminy, for the long pause delays the onset of the ventricular systole for which it provides an impulse. We have no explanation to offer for the phenomenon ; it is illustrated in Fig. 5.

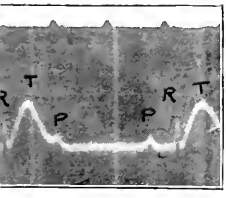
2). The ventricular rate may increase at the onset of complete heart-block. This acceleration demonstrates the relative or absolute inactivity of impulse formation in the ventricle during the preceding stage of 2 : 1 heart-block. The auricular rate meanwhile may remain constant or diminish ; it does not accelerate as does that of the ventricle.

Conclusions.

1. In the experimental animal, as a result of asphyxia, heart-block in the grades in which it is encountered in clinical cases, is of almost


P

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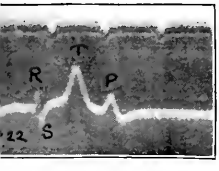
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Fig. 1. I-IV. ½linear. Cat 1, observation 1. Four electrocardiograms from a single period of asphyxia. Taken from a decapitated and atropinised cat. They show varying grades of heart block in the order of their onset, in the fourth observation upon this particular animal. The time-signal is 0·2 sec. in all figures. The P R intervals are marked in sec.

I. Curve taken 1 min. after the onset of asphyxia. The P R interval is 0·08 sec.

II. Curve taken 5 min. 30 sec. after onset. The P-R interval, which first showed increase 4 min. 15 sec. after onset, is 0·12 to 0·13 sec.

III. Curve taken 6 min. after onset. 2 : 1 heart block is present. The P R interval is 0·15 sec.

IV. Curve taken 7 min. 30 sec. after onset. Complete heart block is present.

The heart subsequently recovered its original rate, and the heart block disappeared with the restoration of respiration.

Fig. 2. ½linear. Cat 5, observation 3. A curve taken soon after the onset of asphyxia, from a decapitated cat. It shows two dropped beats and the lengthening of P R interval which leads up to them and shortening of P R interval succeeding them. Certain of the auricular systoles (P) fall back on the preceding ventricular systoles (R and P). The P R intervals are marked in sec.

Fig. 3. ½linear. Cat 10, observation 2. Curve taken from an intact cat, 3 min. after onset of asphyxia, vagi intact, under urethane and curare. Showing dropped beats and the prolongation of P R intervals leading up to them.

Fig. 4a. ½linear. Cat 10, observation 3. From the same cat. Showing the rapid recovery to 2 : 1 heart block. (Asphyxia with succeeding figure.)

Fig. 4b. ½linear. Cat 10, observation 3. A top of curve of 1 sec. duration has been excised between curves 4 and 4 b. The P R interval is now 0·08 sec.

Fig. 5. ½linear. Cat 10, observation 7. Subsequent to the recovery shown in Fig. 4 a and b the vagi were cut and the cat underwent four further asphyxial periods, in two of which complete heart block was developed. The curve is given to show the complete recovery of conduction succeeding this dissociation.

Fig. 6. ½linear. Cat 1. Alternation of the P R interval. A strip of curve lying between periods of 2 : 1 heart block.

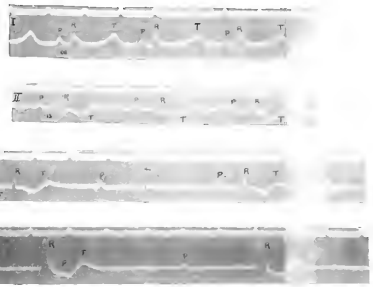

Fig. 1

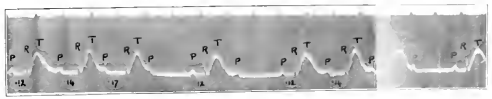

Fig. 2

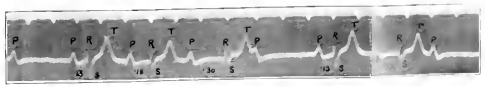

Fig. 3

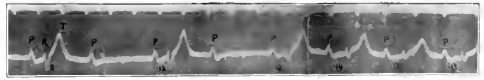

Fig. 4a

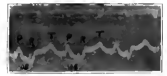

Fig. 4b

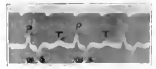

Fig. 6

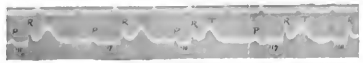

Fig. 5

regular occurrence. It commences within a few minutes of the cessation of ventilation, and is first manifested by a change of conductivity, a lengthening of the auriculo-ventricular systolic interval. It is observed in the intact curarised animal, with or without vagal section, in the decerebrate and the spinal animal, and after atropinisation.

2. All grades of heart-block, even complete, may be succeeded by speedy and complete recovery of conduction.

3. The heart-block is accompanied by a marked retardation of the auricular rate, and this likewise is independent of inhibitory influences.

4. Alternation of the P-R intervals, in the absence of dropped beats, is described.

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A STUDY OF THE MODE OF ACTION OF GASTROTOXIN AND THE HEALING OF GASTROTOXIC ULCERS.[1]

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(PLATE XXIII.)

IN a former paper (1) I was able to demonstrate that the serum formed by immunising the rabbit with the gastric cells of the guinea-pig, or with those of another rabbit, on injection into the guinea-pig's peritoneum produced general symptoms of intoxication and patches of necrosis in the mucous membrane of the stomach, which were stained black by altered blood pigment, and which subsequently developed into gastric ulcers.

The present communication will deal with the two following points:—

1. The way in which the blood-stained patches of necrosis are produced.

2. The subsequent changes which occur in the ulcers under normal and pathological conditions.

A preliminary report on some of the main results of this series of experiments was communicated to the Pathological Section of the Royal Society of Medicine in 1908 (2).

I. MODE OF ACTION OF GASTROTOXIN.

The presence in the necrotic patches of altered blood pigment seemed to indicate that the gastric juice played an important part in the production of the lesions, which might have been brought about in one of the two following ways:—

1. By the direct action of the gastrotoxin on the gastric cells, the hæmorrhage being secondary to digestion of the mucous membrane by the gastric juice.

[1] Received December 8, 1909.

2. By a destructive action of the poison upon the capillary wall, the hæmorrhage being the primary condition, and the cell necrosis a secondary effect of the gastric juice.

It was decided, therefore, to put the gastric juice out of action whilst the poison was acting. This is quite easy to do, since the poison acts within a few hours.

The method, which consists in passing a soft rubber catheter down the œsophagus of the guinea-pig and filling its stomach with a weak alkaline solution, and the results of this experiment, were described in a former paper (1907 [3]). It was found that neutralisation of the gastric juice prevented the occurrence of any lesion in the stomach. The alkaline solution employed had a volume of about 14 c.c. to 20 c.c., and contained 1 per cent. sodium bicarbonate or any strength above this. Solutions of soda of strengths below 1 per cent. will partially, but not completely, prevent the necrosis occurring. Control animals were in each experiment injected with the same dose of the same serum and in all cases showed the usual lesions.

It was quite evident from these experiments that the first hypothesis was correct, and that the hæmorrhage was a secondary condition, because, if the hæmorrhage had been the primary lesion, neutralisation of the gastric juice would not have prevented its occurrence.

The gastrotoxin therefore directly produces some change in the gastric cells, leading to digestion of the mucous membrane in patches, which are stained dark brown or black by hæmatin formed from the hæmoglobin of the blood in the capillaries by the action of the acid of the gastric juice.

Initial Change in the Gastric Cells.

A series of animals was injected with the serum and the animals were killed at different stages (*e.g.* at the end of one hour, two hours, and so on), so as to obtain microscopic sections of the necrotic patches in the course of formation.

Some of the blocks were hardened in formalin, and the sections stained with hæmatoxylin and eosin. Others were fixed in a mixture of picric acid, formalin, and acetic acid, and the sections stained with eosin and toluidin-blue, or with saffranin, or fuchsin. No distinct change, however, in the cells preceding digestion could be found. All the cells around a necrotic patch which were about to be attacked stained perfectly well and appeared quite normal.

Sections of stomachs in which the gastric juice had been previously neutralised showed the cells to be normal, although the animals had been killed by the serum.

It is evident, therefore, that the actual necrosis of the cells, as seen under the microscope, is brought about by the action of the gastric juice acting upon a cell in some way changed, but showing no microscopic deviation from the normal. With regard to the nature of this change in the cells rendering them susceptible to the action of the gastric juice, two hypotheses present themselves as follows:—

1. The normal cells possess a specific resisting power (possibly of the nature of an antibody), which is destroyed by the gastrotoxin.

2. The cells are damaged or in some way devitalised, and therefore are unable to resist the action of the gastric juice.

In order to settle which of these hypotheses was correct I tested the action of other poisons.

In a previous paper (1906 [4]) I was able to show that hepatotoxin, enterotoxin, and hæmolysin were all able to produce necrosis of the mucous membrane of the stomach indistinguishable from that produced by gastrotoxin. In the same paper it was pointed out that none of these cytotoxins was strictly specific, but that each acted with greatest intensity upon the tissue against which it was formed whilst possessing a slight action upon other tissues of the body. I have now been able to show that the above three cytotoxins produce their effects upon the stomach in exactly the same way as does gastrotoxin. This was shown by the method of neutralisation of the gastric juice by sodium bicarbonate. In all the cases the alkali was able to prevent the stomach lesions occurring; thereby showing that the poisons acted directly upon the stomach cells and did not cause ulceration by first producing a hæmorrhage. I referred to this fact in the paper published in December 1908, and in June 1909 Rehfuss ([5]), using my neutralisation method, proved that the venom of *Heloderma suspectum* produced gastric ulceration in the same way.

It seems quite clear from this that the second hypothesis is correct, namely, that it is a question of devitalisation of the cell, which then becomes digested, for hepatotoxin, enterotoxin, and hæmolysin cannot be supposed to have any influence in removing or destroying any supposed specific resisting power possessed by the gastric cells against digestion by the gastric juice. This observation is important from several points of view. It establishes the principle that self-digestion of the gastric mucous membrane may be brought about by a poison circulating in the blood, and it also raises the question whether there may not be many endogenous and also exogenous poisons (*e.g.* bacterial or otherwise) which by their action on the gastric cells through the blood stream may so devitalise them as to initiate self-digestion. Whether the cell is actually killed by the poison or not does not seem to me of much importance. The point is that the cell can be so altered by a poison circulating in the blood that it is digested.

It is well known that acute gastric ulcer in the human being is associated with many different diseases of bacterial origin, and that necrosis of the gastric mucous membrane may be brought about by bacterial poisons irrespective of the actual presence of the micro-organism, as in Péron's case (1897 [6]) and in the experimental work of Enriquez and Hallion (1893 [7]), to quote instances. Many bacteria on injection give rise to ulceration of the stomach, and a great deal of

work has been done in this direction, but the details of this do not concern us here.

These experiments also show that a hæmolytic serum prepared by the injection of washed red blood corpuscles probably contains many protoplasmic poisons, for in addition to its actions upon the red blood corpuscles, and upon the capillary wall by its hæmorrhagin, it is also able to damage the gastric cells. It does this although no hæmorrhages are to be found anywhere in the body, the capillary endothelium not being sufficiently damaged to allow of the escape of blood, the gastric cells being necrosed because they happen to be exposed to the action of the acid gastric juice. It is not intended in this short report to discuss fully the literature on the subject, and it is sufficient to state that it is now well known that hæmolysin will act on many tissues of the body.

This demonstrated action upon the gastric cells of a poison circulating in the blood suggested that certain substances introduced into the cavity of the stomach might produce a similar effect, or, if too weak to produce self-digestion alone, that they might, if combined with the administration of gastrotoxin, increase the effect produced by this poison.

Effects of Hyperacidity of the Gastric Juice.

The first substance experimented with was hydrochloric acid. The *normal acidity* of the stomach contents of the guinea-pig was estimated at varying periods of time after it had eaten a test meal of oats, bran, and green vegetables.

The animal was killed, and the stomach contents made into a suspension with 50 c.c. distilled water. The volume of the contents was thus determined. The suspension was diluted with water until its volume formed a simple multiple of that of the stomach contents. The suspension was allowed to stand for twelve hours and then filtered. The percentages of the total chlorides and of the inorganic chlorides in the filtrate were determined by the silver nitrate method, and the percentage of active HCl found by deducting the latter from the former. By this method the following results were obtained in twelve animals:—

Time after Test Meal.	Percentage of Active HCl.
1 hour	0·126, 0·1008.
2 hours	0·144, 0·09, 0·108, 0·126, 0·144.
3 ,,	0·216, 0·234, 0·187.
4 ,,	0·252, 0·205.

The increase in acidity is due to the fact that a guinea-pig eats a very large test meal in a short time if previously starved, so that the food does not become uniformly saturated with acid till about three hours after the meal. The amount of HCl is very similar to that found in the human subject.

Effects of Hyperacidity of the Gastric Juice alone.

Twenty-four guinea-pigs were fed with solutions of HCl of various strengths by stomach tube, the animals having been previously starved overnight. It was found that no effect was produced with solutions up to a certain point, but beyond this point necrosis of the mucous membrane and ulceration were produced, the lesions macroscopically differing in no particular from those produced by gastrotoxin.

The acid used was commercial HCl, which by titration with decinormal soda solution was found to contain about 34 per cent. HCl. About 20 or 25 c.c. of the solutions were introduced in each case. The weights of the animals varied from about 300 to 600 grms.

The results obtained were very uniform. Solutions of strengths below 0·7 per cent. HCl produced no lesion in any animal, small or large. Above 0·7 per cent. lesions occurred in the smaller animals, and above 0·9 per cent. in the larger animals. Solutions of 1, 1·16, and 1·3 per cent. strengths converted the whole mucous membrane into a black mass.

Effects of Hyperacidity combined with Gastrotoxin.

A series of twenty-two experiments was done in the same way as I described in connection with the neutralisation experiments. The dilute acid solution was introduced into the stomach by an œsophageal tube, and the gastrotoxic serum at once injected into the peritoneal cavity. In each experiment a control guinea-pig was injected with the same amount of the same serum at the same time, and the two experiments subsequently compared.

In my first paper (1904 [1]) I pointed out that the lesions produced by gastrotoxin were not invariably of exactly the same extent in guinea-pigs of the same weights, but this error becomes negligible when a sufficient number of experiments is done.

The strengths of the HCl solution in each case were such as had been found to be innocuous alone (*e.g.* below 0·7 per cent.). Solutions of strengths above 0·3 per cent. were found to increase markedly the lesions; below this strength the result was sometimes an increase, and at 0·2 per cent. the solution produced no effect whatever. Three of these experiments were described in the paper quoted above (1907 [3]), the HCl referred to in that paper being commercial HCl. This result indicates that if the percentage amount of HCl in the stomach contents of the guinea-pig rises above normal, the lesions produced by gastrotoxin will be more marked than if the acidity of the stomach contents be normal.

How does the Hyperacidity produce this Effect?

In answer to this question two hypotheses are available—

1. The HCl increases the peptic activity of the gastric juice.
2. The HCl acts as an additional protoplasmic poison.

The first hypothesis is unlikely, because it is well known that only within small limits will an increase of HCl assist in the digestion of certain food-stuffs. There is a definite amount of acidity for optimum activity of the gastric juice, and this varies for the different

kinds of protein to be digested. The whole question probably turns on what strength of acid will most easily cause swelling of the tissue to be digested. It seems, therefore, that the second hypothesis is correct, and that the HCl increases the tendency to digestion of the mucous membrane by acting as a protoplasmic poison. In the higher strengths (*e.g.* above 0·7 per cent.) it is able alone to poison the gastric cells and bring about self-digestion; in the lower strengths (*e.g.* below 0·7 per cent.) it adds its quota to that of the gastrotoxic serum, and the result is a summation of effects.

This hypothesis is supported by certain experiments in which I have introduced other protoplasmic poisons into the guinea-pig's stomach.

These experiments will now be considered.

Effects of the Introduction of other Acids alone.

Three acids have been used—commercial sulphuric, glacial acetic, and lactic acids. These were introduced into the stomach by œsophageal tube under the same conditions and in the same amounts as in the case of the HCl.

Commercial sulphuric acid.—Black patches of necrosis are produced with all strengths above 0·9 per cent.; below this no lesion results.

Glacial acetic acid.—Necrotic patches and ulcers are produced by a 2·5 per cent. solution, and solutions of all strengths above this. A 2 per cent. (and below this) solution produces no lesions.

Lactic acid.—This acid is not so potent as the former. In all guinea-pigs no lesion whatever results when 4 per cent. or weaker solutions are used. Solutions of 6 per cent. strength or above this cause lesions in small animals (400 grms.). Larger animals require a rather higher percentage. The whole mucous membrane may be brown in colour, with distributed black patches.

Effects of these Acids combined with Gastrotoxin.

The strengths of the acids used were such as had been found to be innocuous alone. The acids were introduced into the stomach as before, and gastrotoxin was at the same time injected into the peritoneum. Controls were in all cases injected with the gastrotoxic serum.

Commercial sulphuric acid.—Solutions of 0·6, 0·7, and 0·8 per cent. strengths increase the lesions produced by gastrotoxin, but 0·5 per cent. and under appear to have no effect.

Glacial acetic acid.—A 0·5 per cent. solution or any strength above this markedly increases the gastrotoxic lesions.

Lactic acid.—3 and 4 per cent. solutions increase the effect of gastrotoxin.

Effects of Acids combined with Hepatotoxin, Enterotoxin, and Hæmolysin.

Briefly stated, it has been found that the acids in inert solutions increase the effects produced by these three cytotoxins in exactly the same way as they do those of gastrotoxin.

Effects of the Introduction of other Protoplasmic Poisons.

Bile salts and formic aldehyde were used. They are powerful protoplasmic poisons, and produce much the same effect upon the mucous membrane

of the stomach. The lesions produced are quite different from those caused by acids. The stomach is found to be much congested, the mucous membrane is dull red and raw looking, and there is considerable secretion of mucus. With weaker solutions a black patch or two may be seen. Digestion of the mucous membrane does not occur, because the cells are probably protected by the increased secretion of mucus, and probably also by stoppage of the secretion of gastric juice.

Sodium taurocholate produces the above effects in 3 per cent. solution. Combined with gastrotoxin inert solutions commonly cause a marked inflammatory reaction; if this does not occur the gastrotoxic lesions are increased (Plate XXIII. Fig. 1).

The weakest strength of *formic aldehyde* which is able to produce such lesions is 0·3 per cent. Combined with gastrotoxin inert solutions produce precisely the same effects as does sodium taurocholate.

From all these experiments it appears that self-digestion of the mucous membrane of the stomach may be brought about by poisons devitalising the gastric cells, either through the blood stream or by attacking them from the free surface of the mucous membrane, and that in either case the lesions produced are precisely the same. It is of great significance that certain substances, in themselves innocuous when introduced into the stomach, are, however, able to add their quota to that of a devitalising influence affecting the cells through the blood, and so produce self-digestion. This is of special importance in relation to hydrochloric acid, since any increase above the normal markedly predisposes to self-digestion. The percentage of HCl in the human stomach rarely rises above 0·35 per cent. But the *total acidity* may rise to 0·6 or 0·7 per cent., and it has been demonstrated that other acids besides HCl (lactic, etc.) are also able to produce a devitalising influence on the gastric cells, so that here is a condition especially predisposing to self-digestion. Again, vinegar contains 4 per cent. glacial acetic acid, and 0·5 per cent. solution of this acid is capable of increasing the gastrotoxic lesions, so that the drinking of vinegar, which is occasionally seen in a certain class of persons, is quite likely to cause gastric ulceration, especially if associated with some poisoning of the cells through the blood.

The fact that the above acids are able to increase the devitalising action of gastrotoxin lends support to the view that the latter substance does not actually kill the gastric cells, but markedly affects their vitality. It is, of course, difficult to prove this point, but it certainly appears as if the actual death of the cell were not a necessary antecedent to digestion.

II. The Healing of Gastrotoxic Ulcers.

It has been shown that gastrotoxin is not a specific poison for the gastric cells, but that it acts on other tissues and produces general symptoms of intoxication. The method of injection into the peritoneal cavity or blood stream is therefore an unsuitable one to employ for

the study of the changes occurring in the ulcers, because so many animals die from the effects of the poison upon other tissues. It is of no use giving small doses, as the poison is taken up by so many organs of the body that it is soon neutralised, and I have shown that repeated injection of the serum gives rise to immunity to the gastrotoxin ([3]). I have therefore used the method of local injection of the serum into the stomach wall, and in this way a true acute gastric ulcer, in all respects comparable to that seen in the human subject, may be produced.

Method.—The guinea-pig is previously starved for some fifteen or eighteen hours, so that the stomach wall is not too thin and the stomach can be properly manipulated. The organ is by no means empty, and after this period of starvation it usually contains variable amounts of highly acid food remnants. If the stomach were absolutely empty and the glands resting it is probable that ulceration would not be produced, as the necrosis of the epithelium depends upon digestion by the gastric juice.

Ether is administered, the abdomen is opened in the middle line under strict antiseptic precautions, and the stomach drawn out. A hypodermic needle is inserted under the peritoneal coat of the stomach, and from $1\frac{1}{2}$ to 2 c.c. gastrotoxic serum injected so as to form a blister under the peritoneum. The size of this blister should not be less than that of a shilling. More or less serum escapes when the needle is withdrawn, but not much, as it is enclosed in the meshes of the tissues, forming a local œdema. The stomach is replaced and the abdominal muscles and peritoneum united by silk, the skin being separately sutured. A collodion dressing is applied, and the wound heals by first intention.

Mode of action.—I have been able to show that the action is a toxic one, and not a mechanical effect resulting from pressure. In order to do this it is merely necessary to inject an innocuous fluid and note the result. I have injected normal rabbit's serum, normal guinea-pig's serum, and physiological salt solution. In each case the solution is absorbed without leaving any trace of necrosis or ulceration.

It is, of course, possible to produce slight mechanical ulceration by injecting massive amounts of neutral fluids, and this is easier to do in the case of normal rabbit's serum, because it is very slightly toxic for the guinea-pig's tissues, but it is surprising to what an extent the mucous membrane and peritoneal coat may be separated without any harm whatever resulting; such a method of producing ulceration is, however, quite useless, as one can never predict what is likely to happen, the whole may be completely absorbed, the mucous membrane may rupture, a slight ulcer may result, or the animal may die.

The activity of the gastrotoxin in producing an ulcer by the method of local injection varies exactly with its activity in producing lesions when carried to the stomach by the blood. As I have mentioned before, individual rabbits vary in the strength of the serum they produce. The best time for collecting the serum for this purpose is, as I have pointed out in former papers, from four to six weeks after

the commencement of immunisation, and after a few months the serum is not of much potency.

Formation.—The gastrotoxic serum soaks into the overlaying mucous membrane, which is then digested at this spot by the gastric juice and forms a slough. There is always more or less hæmorrhage under the mucous membrane, which depends on mechanical injury to the vessels during the injection. By about the third or fifth day the necrosed portion has become disintegrated and separated, and a clearly defined ulcer is formed having for its base the peritoneum, which is more or less covered with the remains of the muscular coat. There is no doubt that the necrosed tissue becomes secondarily infected with bacteria from the food, and that in this way adhesions with neighbouring organs and thickening of the base of the ulcer is produced; at the same time irritation of the base of the ulcer by the gastric juice may probably produce a like result. The size of the ulcer is considerably less than the size of the blister which has been produced in the first instance. During the formation of the ulcer the peritoneum may give way and septic peritonitis result, or it may become adherent to the liver or other organ and a subdiaphragmatic abscess result.

Healing.—The healing was first studied in animals on a normal diet (oats, bran, and green vegetables). The conclusions have been drawn by observing the different stages in the healing in some forty guinea-pigs. A certain number of the animals died during the formation of the ulcers as described above. In all the cases the ulcer was produced upon the anterior wall of the stomach at about its centre. The ulcer commences to heal at once, and gradually shrinks, becoming smaller and smaller until it is completely healed.

Sometimes there is practically no thickening left, the ulcer having disappeared except for a slight puckering of the mucous membrane, which may have a stellate character. At other times there is considerable thickening of the peritoneum, and a definite nodule is left to mark the site of the ulcer. The base of the scar may be firmly adherent to a neighbouring structure, or loose and completely organised adhesions may occur with the intestines, omentum, liver, and abdominal wall. In all cases the ulcer heals in from fourteen to twenty-eight days. The actual time of healing depends to a large extent on the size of the ulcer, and probably upon the amount of inflammatory reaction set up, which in its turn may depend upon the extent to which the ulcer has been secondarily invaded by bacteria or irritated by the gastric juice. It is impossible to make all the ulcers of exactly the same size, since the serum does not always spread out over exactly the same area, and more escapes from the puncture in some cases than in others, so that a slight variation occurs in the exact time of healing; but this only amounts to a few days, and I repeat that in all cases healing promptly occurs.

Cohnheim ([8]), using a modification of a method first introduced by

Panum (1862 [9]), found that the gastric ulcers, produced in dogs by injection of chromate of lead into one of the gastric branches of the splenic artery so as to give rise to an area of infarction, healed within three weeks. Many other experimenters, from Quincke ([10]) in 1875 to Litthauer ([11]) in 1909, have directly injured the gastric mucous membrane by various means, and also found that the lesions so produced healed within a few weeks. Acute ulcers of the stomach are by no means uncommon in the human subject; they do not necessarily give rise to symptoms, and they heal as experimental ulcers do. Chronic gastric ulcer, however, is a common malady, the ulcer may persist for months or even years, and it may extend.

Since ulcers formed by the process of self-digestion are initially acute, there must be present some unknown condition or conditions preventing the healing of such chronic ulcers. I have performed the following experiments with the object of discovering such conditions.

Effects of position.—I have produced ulcers quite close to the *cardiac orifice* in nine guinea-pigs and have found that, the animals being otherwise normal, the ulcers all healed up in about three weeks.

Pyloric ulcers were formed in ten animals, and were found to heal up in precisely the same time. Whether the serum be injected into the *anterior* or *posterior* wall does not at all matter, the resulting ulcers heal up in the prescribed time.

Effects of hyperacidity of the gastric juice.—Ulcers were produced in twenty-four guinea-pigs. Half the animals were put on a normal diet and half on an acid diet. The animals were killed at various stages, and in each case the stomachs of those on an acid diet were compared with those on a normal diet.

This investigation showed that the ulcers in the animals fed on an acid diet passed through precisely the same stages as those in the animals fed on a normal diet, and that they healed up in the same time. On the whole, they appeared to be in a rather more advanced condition of healing than the corresponding ulcers in the animals fed on a normal diet. The acid diet consisted of green vegetables, bran, and oats soaked in 2 per cent. commercial HCl (1 = 0·6 per cent. HCl) (Plate XXIII. Fig. 2). The animals do not like this food, but they will eat it when they are hungry.

In order to show that it is possible to keep the percentage of HCl in the gastric contents above the normal by this means a series of animals was fed on food soaked in 0·5 per cent. HCl and the stomach contents estimated each hour, with the following result:—

Time after Test Meal.	Percentage of HCl.
1 hour	0·3240
2 hours	0·2793
3 ,,	0·234
4 ,,	0·2916
5 ,,	0·3168

Five animals in which pyloric ulcers had been produced were put on food soaked in HCl combined with albumin. The ulcers of these animals passed through the usual stages, and healed during the third week.

A moderate increase in the acidity of the gastric juice such as occurs in the human being will not therefore delay the healing of an ulcer. Several observers, especially Matthes (1893 [12]), have been credited with proving that hyperacidity delays the healing of an ulcer. Matthes only describes one experiment in which he stitched a porcelain ring to the peritoneal layer of the stomach and cut off the enclosed mucous membrane measuring 6 cm. in diameter. The dog was given a 0·5 per cent. solution of HCl daily by tube, and at the expiration of three weeks was killed. An unhealed area the size of a split-pea was found at the autopsy. The lesion of the control animal was healed in four weeks. The evidence afforded by this experiment of the influence of hyperacidity in delaying the healing of an ulcer does not appear to me to be very weighty, especially in view of the recent experiments of Litthauer (1909 [11]), who found hyperacidity without influence.

Gastric ulcer in the human being may or may not be associated with hyperacidity of the gastric contents.

It has been shown above that hyperacidity of the gastric contents is capable of increasing the tendency to ulceration, and since it has been shown that hyperacidity will not of itself delay the healing of gastric ulcer in the guinea-pig, it seemed of interest to determine what was the effect of the presence of gastric ulcer upon the acidity of the gastric juice.

Effects of Acute Gastric Ulcer upon the Acidity of the Stomach Contents.

Ulcers were produced in nineteen guinea-pigs. These animals were given test meals at various stages of the healing process, and the stomach contents were examined two hours later. The normal percentage of HCl two hours after a test meal as stated above is from 0·09 to 0·144. The following results were obtained :—

Day of Disease.	Condition of Ulcer.	Percentage of Active HCl.
5	Large, necrotic, base tore	Nil.
5	Small, clean base	0·2772
6	Large, necrotic, base tore	0·036
6	Large, sloughy base, adherent	0·054
6	Medium, clean	0·108
7	Large, sloughy base	0·0576
8	Large, slough, small abscess	Nil.
8	Large, adherent, thickened, clean	0·0972
8	2 pin-point, almost healed, ulcers	0·09
9	Large, clean	0·1872
10	Small, adherent, base tore	0·07
11	Medium, adherent, clean	0·144
11	Pin-point, almost healed	0 144
11	Medium, base necrotic	0·126
14	Large, clean	0·216
14	Medium, clean	0·324
18	Small, adherent, almost healed	0·144
19	Small, almost healed	0·144
20	Healed, thickening	0·18

It appears that when the ulcer is in the stage of formation and before the base has been cleanly digested there is a diminution in the active HCl in the gastric contents. If this were due to neutralisation of the HCl by the alkaline discharge from the ulcer the inorganic chlorides would be correspondingly increased.

As a fact in the above experiments the inorganic chlorides remained about normal in all cases, and there was no such correspondence to be seen; so that in the early stages there is a diminished secretion of HCl. When the base of the ulcer is clean and it is in process of healing there may be an increase in the HCl secreted, but it is more likely that the HCl will be normal in amount, especially if the ulcer be almost healed.

Effects of Diminution of the Acidity of the Gastric Juice.

Gastric ulcers were produced in twenty-five guinea-pigs, and the animals were then placed on an alkaline diet consisting of oats, bran, and green vegetables soaked in 4 per cent. solution of sodium bicarbonate. The ulcers in these animals were compared with controls at various stages. In all cases the ulcers showed evidence of healing, but in the early stages there was perhaps more sloughy material attached to the base of the ulcers, and in the later stages slightly more tendency to thickening and adhesions than in the animals on a normal diet. In many cases the ulcers also seemed to be in not quite such an advanced stage of healing as were the control ulcers.

However, if any delay occurred in the healing process it was only a question of a few days, and in no case did a chronic ulcer result. I have mentioned above that when the gastric juice is hyperacid the ulcers appear to heal more rapidly; this is probably due to the fact that the food is better disinfected. When the acidity of the gastric juice is diminished the food is not so well disinfected and there is a greater tendency to bacterial infection, and perhaps a slight lengthening of the healing time, but this is of no material importance. Diminished acidity of the stomach contents probably also leads to a loss of tone in the muscular coats, which may be of some influence.

The following table shows that it is possible to keep the gastric contents alkaline or neutral for longer periods of time than are normal by feeding animals on food soaked in soda solution, although it is impossible by this means to render the contents permanently alkaline. The animals were fed on food soaked in 4 per cent. sodium bicarbonate solution, and the stomach contents examined at different intervals.

Time after Test Meal.	Percentage of HCl.
1 hour	Absent.
2 hours	,,
3 ,,	,,
4 ,,	0·072.
5 ,,	0·2016, 0·126, 0·252.

As a matter of fact, at any period of digestion, although the contents of the stomach are alkaline, there is always a layer in contact with the

stomach wall giving an acid reaction; when the contents are mixed for estimation this layer of acid is neutralised by the alkali.

It used to be taught that the giving of an alkali increased the secretion of HCl; later Pawlow showed that it inhibited it.

These experiments appear to indicate, however, that the HCl is merely neutralised by the alkali, forming NaCl till the whole alkali is used up, and then the acidity of the gastric contents becomes normal. So that the only effect is to cause a delay in the digestive process.

Effects of Bacterial Feeding.

The above results suggested that perhaps a secondary bacterial infection of the ulcer might be responsible for its chronicity.

Two series of experiments were therefore conducted. In the first series seven animals, in which ulcers had been produced, were fed on food soaked in fresh cultures of *Bacillus pyocyaneus*, and the ulcers compared with those of control animals.

In the second series six animals, in which ulcers had been produced, were fed on alkaline food soaked in fresh cultures of *B. coli communis*, and their ulcers likewise compared with those of control animals fed on a normal diet.

In both series of experiments the ulcers healed as usual, whether the animals were fed on normal or infected diet, and no chronic ulcer ever resulted. In the animals fed on *B. coli* there were perhaps more thickening and adhesions than in those fed on normal diet.

It appears, therefore, that so long as the stomach empties itself in the normal time, or, in other words, so long as there is no motor insufficiency, it is impossible to affect the healing of a gastric ulcer materially by an alteration in the acidity of the gastric juice such as occurs in the human subject or by feeding on moderately infected food.

Conclusions.

1. Gastrotoxic serum damages functionally the gastric cells, and the actual necrosis and ulceration of the mucous membrane is brought about by the gastric juice, the process being one of self-digestion.

2. All the other cytotoxic sera examined are capable of damaging the gastric cells in a similar manner, but to a less extent, and of initiating self-digestion.

The possibility is therefore established that certain endogenous poisons, and probably also certain exogenous poisons (*e.g.* bacterial poisons, and so on), may exist in the blood and be capable of so devitalising the gastric cells as to initiate self-digestion. An endogenous poison, potentially able to attack the stomach of the animal forming it, may be produced, as I have proved, by immunising the rabbit with rabbit's gastric cells.

3. Certain substances introduced in excess with the food may act in like manner as protoplasmic poisons.

4. These substances, if innocuous alone, are nevertheless capable

of adding their quota to a devitalising influence acting through the blood stream, and of thereby increasing the effect of the latter. Hyperacidity of the gastric juice is able to act in this manner.

5. Acute gastric ulcers heal within a few weeks, whether the gastric juice be normal or increased or diminished in acidity to the extent which may be found in man.

6. The presence of an acute sloughing ulcer in the stomach is associated with a diminution in the acidity of the gastric contents, and when the ulcer is healing the acidity is normal. Hyperacidity may occasionally occur.

7. If the motor power of the stomach be normal, neither *B. pyocyaneus* nor *B. coli communis*, even though the gastric contents be diminished in acidity, are able to delay the healing of gastric ulcer.

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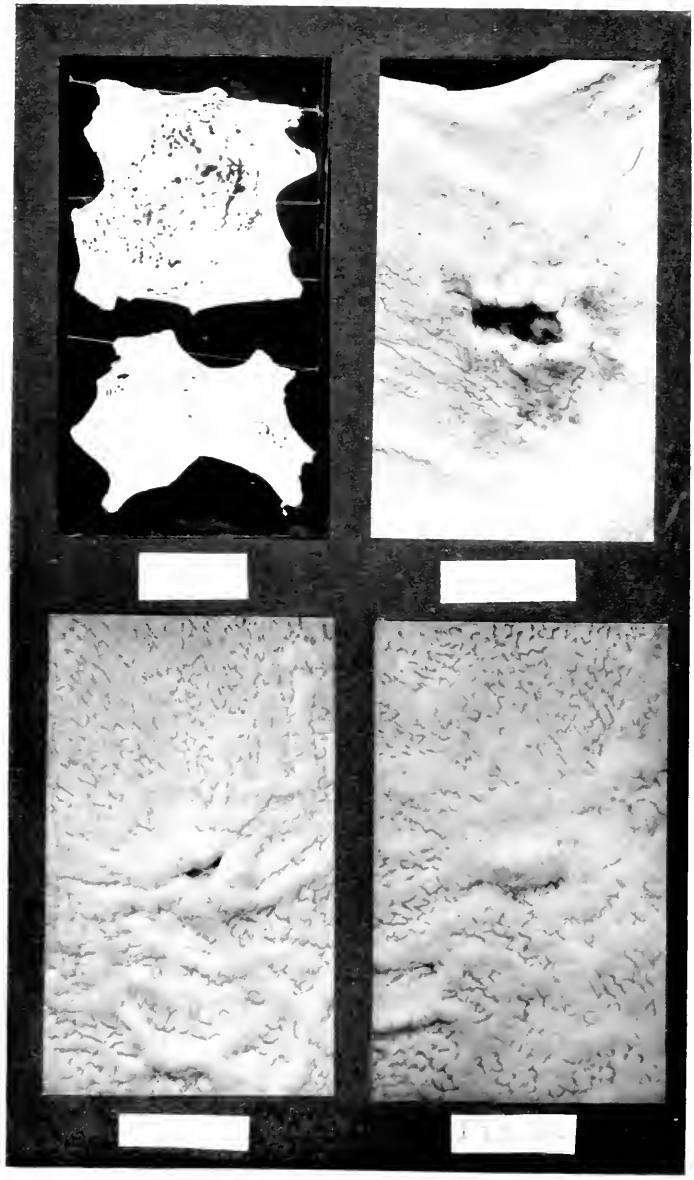
DESCRIPTION OF PLATE XXIII.

Fig. 1.—Demonstrates the influence of bile salts in increasing gastrotoxic lesions in the guinea-pig. *Upper stomach.*—Twenty c.c. of a 1 per cent. solution of sodium taurocholate were introduced into the stomach, and 10 c.c. gastrotoxic serum then injected into the peritoneum. Marked necrosis. *Lower stomach.*—Control animal. Ten c.c. gastrotoxic serum were injected into the peritoneum. Slight necrosis.

Fig. 2.—Illustrates the healing of gastric ulcer in the guinea-pig on a hydrochloric acid diet (0·6 per cent.). (*a*) *Sixth day.*—There is a little altered blood at the base of the ulcer, and a little bruising around it. (*b*) *Thirteenth day.*—A small triangular-shaped ulcer, which is rapidly healing, is present. (*c*) *Fourteenth day.*—A small nodule of fibrous tissue is all that remains.



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PAROXYSMAL TACHYCARDIA, ACCOMPANIED BY THE VENTRICULAR FORM OF VENOUS PULSE.

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The ventricular form of jugular pulse may be defined as a type of venous pulsation, in which no constant and prominent waves present themselves, at such periods as represent the diastoles of the ventricle.

It has been regarded as significant of the absence of auricular contraction during the diastole of the heart; but it is now known that it may be found where the auricular systole, falling at its proper instant during the cycle, fails to affect the venous pressure appreciably or at all.[2] The events occurring in the auricle when the venous pulse is of the ventricular form cannot be gauged from this type of pulsation itself; for when it is present the mechanism of the auricle may be one of the following forms:—

1. Contraction, at the normal instant in the cycle, of an auricle which is in a state of distension, or the power of which is damaged in some other fashion.
2. Fibrillation of the auricle.
3. Simultaneous contraction of auricle and ventricle.

In a previous communication[2] the relationships of such abnormal auricular activities were discussed, and certain conclusions were formed in regard to them.

At that time it seemed clear that auricular fibrillation is never accompanied by regularity of the ventricle, except when it is complicated by auriculo-ventricular heart-block; and it appeared reasonable to assume that, where the ventricular form of venous pulse is present *and the pulse is regular* and of normal or increased rate, the auricle is not in a state of fibrillation.

The ventricular form of phebogram, associated with *regularity* of the pulse, may conveniently be grouped under three headings:—

(*a*) Where the pulse is slow and auricular fibrillation and heart-block are present.

* An investigation carried out under the tenure of a Beit Memorial Research Fellowship.

(*b*) Where the auricle is distended and its contractions are ineffective in raising venous pressure; the pulse being of normal or somewhat increased rate.

(*c*) Where the pulse is greatly increased.

It is under the last heading that a by no means uncommon type of paroxysmal tachycardia falls, of which a number of polygraphic curves have been obtained (Mackenzie,[5] Hewlett,[1] Lewis[2]). But the interpretation of the mechanism of the heart-beat in such cases has never been more than speculative, for hitherto no electrocardiograms have been won. It has been suggested that paroxysms of *regular* tachycardia, accompanied by the ventricular type of venous pulse, may arise, as a consequence of simultaneous auricular and ventricular systole, either in response to impulses originating in the junctional tissues,[6] or as a result of altered conduction, and the coincidence of an auricular systole with the ventricular systole of a preceding cycle[7]; or, lastly, as the outcome of a ventricular tachycardia retrograde to the auricle.[2]

A case is now described of the type under discussion because it is hoped that it may throw light upon these questions, and in justification of the position adopted, that a rapid pulse which is *regular* is never present when the auricle is fibrillating, even though the ventricular form of venous pulse is found.

I am indebted to Dr. J. Rose Bradford for the opportunity of studying this patient.

The clinical history presents few features which have not been frequently duplicated by previously recorded cases of paroxysmal tachycardia; therefore it is essential to report only the more salient symptoms and signs which were noted.

J. W. was admitted to University College Hospital on April 1st, 1910. A Hebrew of 28 years, and by trade a cook, he was carried to hospital in a critical state, and subsequently gave the following history. Rheumatic fever and chorea, it was stated, had never occurred either in himself or in his family; apart from an attack of typhoid fever several years before admission, he had been healthy. Whilst mounting a flight of stairs he was seized with acute pain in the chest and distress of breathing. The pain was felt over the left half of the chest, the left abdomen, and eventually over the left arm and the left leg. He had never experienced a similar attack and its onset was not foreshadowed.

His condition when first examined gave rise to anxiety. The distress was evident and the collapse considerable. He complained of acute suffering, great pain in the precordial region, shooting into the neck and left arm; a feeling of compression in the lower regions of the chest; and a powerful throbbing in the neck. The skin was pale, cold and moist. He half reclined in bed; restlessness was prominent and he moaned incessantly; salivation was copious and he experienced nausea. The

respirations were rapid and the pulse was counted at between 200 to 210 beats to the minute. Cyanosis was not present. The heart sounds were tic-tac; no murmurs were audible; the dulness was increased to right and left; the impulse was diffuse in the fifth and sixth spaces in the nipple line. The chest was extremely sensitive to slight pressure and friction.

The attack of tachycardia which was present at his admission continued with its accompanying symptoms for eight hours, during which time the liver tended to enlarge, the heart dilated further, and venous engorgement became more evident. The attack ended abruptly and with immediate relief.

The subsequent history of the patient, during his long stay in the hospital, evolves itself into a series of attacks and the intervening intervals of rest. The paroxysms were frequent during the first two months of his stay and their duration varied from a few minutes to 48 hours. His freedom at a later date was attributable to rest, for the crises recurred when he first left bed. A number of the paroxysms originated in straining at stool. The onset was invariably sudden and the offset was always as abrupt. On several occasions the paroxysm ceased within a quarter of an hour of the injection of five drops of Cloetta's digalen or $\frac{1}{100}$ grain of strophanthine; on other and more numerous occasions the drugs were entirely without effect. Many means were resorted to, including ice packs and vagal pressure, but it was impossible to assert that a remedy had been found.

The condition between the paroxysms.

The patient was an extremely neurotic subject, poorly built and indifferently nourished; he presented no physical signs other than those discoverable in the heart. The lungs and abdomen were normal; there was never a sign of dropsy. The heart was enlarged. The right limit lay three-quarters of an inch and the left $4\frac{1}{2}$ inches from the middle line. The first sound was accentuated, the second normal. A distant presystolic murmur was present on many occasions, but varied in distinctness. A thrill was felt at the apex on one occasion only. The mechanism of the heart-beat as portrayed by polygraphic curves is shown in Fig. 1.

The pulse was regular as a rule, though at times when the usual rate of 70 to 80 was reduced to 50, sinus irregularity was noticed. The *a-c* interval was the full 0·2 sec..

The electrocardiograms are shown in Fig. 9, *I*, *II*, *III*. The lead from right arm and left leg (Fig. 9, *I*) is characteristic of mitral stenosis. P is of excessive height and bifurcates. The P-R interval is somewhat increased, measuring 0·18 to 0·20 sec.. In the lead from left arm and left leg (Fig. 9, *II*) R shows a notch on the upstroke. In the lead from right arm and left arm (Fig. 9, *III*) it shows a notch on the downstroke. The

conformation of these curves will be more specially referred to in the sequel. Occasional irregularities were felt at rare intervals, but none were recorded.

The condition during the attacks.

The symptomatology of the patient and many of the physical signs present during the paroxysms have been given. It remains to describe the mechanical and photographic records.

The polygraphic curves.—An example of polygraphic curves is shown in Fig. 2. The venous curve is of the ventricular form, the upstroke of

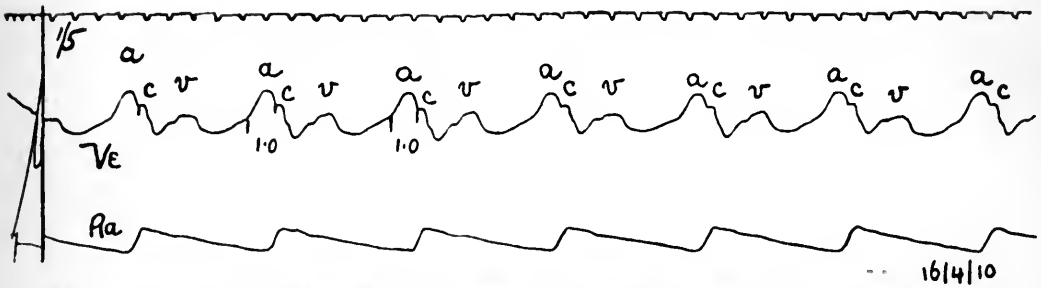

Fig. 1. Polygraphic curves taken during a period intervening between paroxysms, and showing the normal sequence of heart contraction, as indicated by the *a*, *c* and *v* waves in the jugular pulse. The *a*-*c* interval is 0·2 sec.. The time marker in this and succeeding curves is in 0·2 sec..

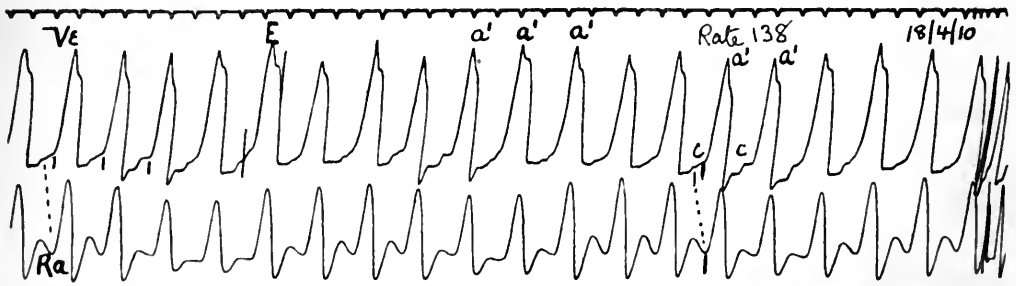

Fig. 2. Polygraphic curves taken during a paroxysm; the rate is 140; the venous pulse is of ventricular form, the large waves marked *a'* fall entirely within the limits of ventricular systole (E). The upstroke of *a'* occurs a little later than the point representing the onset of carotid pulsation.

the high peak coincides with the onset of the radial pulsation, or in other curves falls slightly before it; that is to say, the carotid upstroke falls slightly before or with the upstroke in the venous tracing. The complete wave has a duration of 0·2 sec., a little less than the duration of ventricular

systole as measured in the electrocardiographic curves. The beginning of the downstroke falls approximately at a point calculated as representing the bottom of the dip of the dicrotic in the carotid. The radial pulse is quite regular and markedly dicrotic.

The electrocardiograms.—A number of these curves were taken at different times and with different leads. They are shown in Fig. 9, *IV-VIII*. They are characterised by their regularity from beat to beat. There is no sign of irregular oscillation. Each peak and depression is duplicated from cycle to cycle.

Fig. 9, *I V* shows the curve obtained by leading from right arm and left leg. It consists of a tall peak R of similar duration to that of the similar lead during the slow periods (Fig. 9, *I*). It is succeeded by a deep depression, a further and gradual elevation and a last gradual depression. Then the next beat begins. The lead from left arm and left leg is shown in Fig. 9, *V*. It consists of a peak R, notched on the upstroke (marked ⊙). It is followed by a depression marked T. In no portion of the two preceding photographs is the curve flat; at no point can it be spoken of as isoelectric. The lead from right arm and left arm (Fig. 9, *VI*) presents a peak R with a notch upon the downstroke. It is succeeded by an upright after-swing T. The separate leads were adopted on each and all of the dates which the curves bear, but with the exception of the lead from right arm and left leg, an individual lead showed no conspicuous alteration. Two photographs of the lead from right arm and left leg are given because they are examples of paroxysmal curves at slightly different rates, namely 132 and 168. They differ in that with the faster rate the diastolic portion of the curve is curtailed and in that the latter is straighter with the accelerated heart-beat (Fig. 9, *VII*). A last lead is shown in Fig. 9, *VIII*, and it was taken from the junction of the sternum with the second costal cartilage and from the apex beat.

The interpretation of the curves obtained during the paroxysms.

Before proceeding to a description of the remainder of the tracings obtained from this patient, it will be profitable to discuss the significance of the paroxysmal curves themselves.

The venous curves are of the ventricular form, but two peculiarities call for remark. The excursion is of unusual amplitude and considered alone, the paroxysmal phebograms awaken a suspicion that the forcible venous pulsation, a pulsation readily appreciated with the finger, is not of ventricular origin, for curves of this amplitude and steepness and resulting from ventricular contraction are rarely if ever encountered except where there is great enlargement of the right heart and cavernous distension of the venous tributaries. The question as to whether auricle and ventricle

are contracting simultaneously suggests itself, for when a mechanism of this character is present similar venous tracings are met with.

The second peculiarity is one of less consequence. The upstroke in the venous curve does not coincide with the carotid but with the radial upstroke. This is of lesser significance, for the same time conditions are occasionally encountered, when it can be shown that the auricle is fibrillating.

The electrocardiograms.—Both the radial and electrocardiographic curves clearly show that the mechanism of the heart is regular during the paroxysms; and it may be held, I think with justification, that where a ventricular rhythm is regular the impulses which give rise to it are generated in a single focus. But at the present time I would not use this proposition as an evidence of the nature of the mechanism, for it is more desirable that the case should be utilised in confirmation of the view that, where the pulse is regular and rapid, the auricle is not fibrillating. That such is actually the case is at once evident, for in none of the leads is there any trace of the fibrillatory oscillation. The absence of fibrillation and the similar mechanism from one cycle to the next is shown by the absolute repetition of the individual electric curves; each beat is productive of a similar picture. The rhythm is consequently the result of impulse formation at a single focus, and it remains to locate the seat of this stimulus production. Taking the heart musculature as a whole, a large part of it may be eliminated at once by studying the electrocardiograms. The impulse formation is of supra-ventricular origin. The last conclusion is arrived at from the general conformation of the several curves in the slow and rapid rhythms and their comparison, and especially as a result of an examination of the curves given by separate leads. In the leads from right arm and left leg (Fig. 9, *I* and *IV*) the ventricular complexes differ during slow and fast rhythms respectively in that an inversion of T is present during the latter. A similar change has been reported in experimental auricular tachycardia, and the change is apparently associated with demonstrable conductivity changes in the heart.[3] The slight prolongation of P-R interval (Fig. 9, *I*) is in accord with these observations, and, as will be seen, depressed conductivity was present in other curves from the same patient. (Fig. 10, 11 and 12.) A similar inversion of T is observed in the leads from left arm and left leg (Fig. 9, *V*), but in this figure also the remainder of the curve is a remarkable duplicate of that of Fig. 9, *II*; the notch on the upstroke of R (marked ⊙) is repeated. The resemblance in leads from right arm and left arm is striking (Fig. 9, *III* and *VI*). R and T are of the same type in both slow and paroxysmal curves, and a notch (marked ✲) is present upon both. The general conformation of the curve in Fig. 9, *VI*, is in itself evidence of the supra-ventricular origin of the beat, which gives rise to such a curve; and the special base apex lead from the chest wall (Fig. 9, *VIII*) provides additional support for the view. There is consequently no hesitation in pronouncing

the rhythm of the paroxysm as arising in a part of the musculature which lies above the division of the A-V bundle, and attention may be henceforth confined to the bundle itself and to the auricular tissue. Before pursuing the subject of localisation, the remainder of the curves will be described.

The curves obtained at the termination of the long paroxysms.

The four *polygraphic curves* (Fig. 3-6) were taken at one sitting and within a few minutes of each other; the end of a paroxysm of several hours' duration is shown in Fig. 3. It is succeeded by three brief runs of the quick beats, with a return to the normal sequence in each instance. A similar mechanism is shown in Fig. 4, which is a continuation of the last curve. At the end of the tracing a paroxysm, approximately 10 minutes in length, has its onset. At its termination the two remaining curves were secured. Fig. 5 and 6 are examples of the slow normal rhythm, interrupted by premature beats.

In the investigation of all cases of paroxysmal tachycardia the end curves are of the utmost value and throw considerable light upon the nature of the disorder with which the heart is affected. As in previously reported cases, so in this patient, the paroxysms end in post-paroxysmal pauses, the duration of which is an indication of the ectopic character of the new rhythm. The normal stimulus production has been disturbed by the interference of pathological impulse formation at a point distant from the pacemaker. The end pauses of the long paroxysm shown in Fig. 3, and of the short paroxysms succeeding it, are of duration $\frac{5}{5}\cdot\frac{7}{5}$ to $\frac{5}{5}\cdot\frac{8}{5}$ sec. in the radial curve (the auricular pauses are $\frac{3}{5}\cdot\frac{4}{5}$, $\frac{3}{5}\cdot\frac{9}{5}$, $\frac{4}{5}\cdot\frac{0}{5}$, $\frac{4}{5}\cdot\frac{0}{5}$ sec.). The majority of the ventricular pauses following single premature beats (Fig. 5 and 6) are of duration $\frac{5}{5}\cdot\frac{5}{5}$ to $\frac{5}{5}\cdot\frac{9}{5}$ sec. (the corresponding auricular pauses $\frac{3}{5}\cdot\frac{9}{5}$, $\frac{4}{5}\cdot\frac{0}{5}$, $\frac{3}{5}\cdot\frac{6}{5}$, $\frac{4}{5}\cdot\frac{4}{5}$ sec.). The mechanism though lacking absolute regularity is similar in one case and the other. Following the paroxysms and following the single premature beats, the length of the pause in the auricular curves is greater than the distance between adjacent beats of the normal rhythm in Fig. 5 and 6 (the latter varies from $\frac{3}{5}\cdot\frac{0}{5}$ to $\frac{3}{5}\cdot\frac{5}{5}$ sec.).

The venous curve shown in Fig. 3 is of particular value, for it allows a comparison of the amplitude of the paroxysmal curves and the *a* and *c* waves accompanying beats in which the contraction is sequential. The second ventricular beat which follows the post-paroxysmal pause probably belongs to the normal rhythm; it is followed by four premature beats, each accompanied by a tall venous wave marked *a'*. Now it is evident that these waves are not of purely ventricular origin for the remaining *c* waves of the curve are extremely insignificant. It is rational to assign to them a new factor of production, and the increased amplitude can be explained by supposing that a premature auricular contraction has occurred.

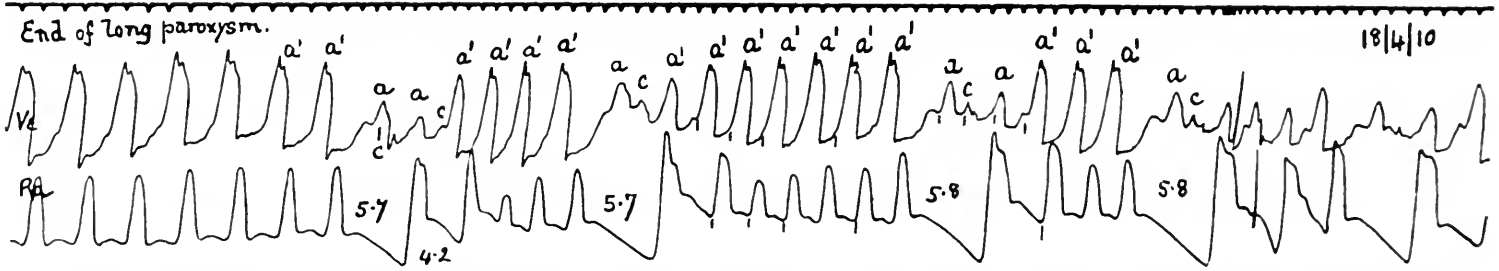

Fig. 3. Polygraphic curves showing the termination of a long paroxysm of the same nature as that shown in Fig. 2. The end of the paroxysm is marked by a pause at the return to the normal sequence, and is followed by the occurrence of three short paroxysms of a similar character.

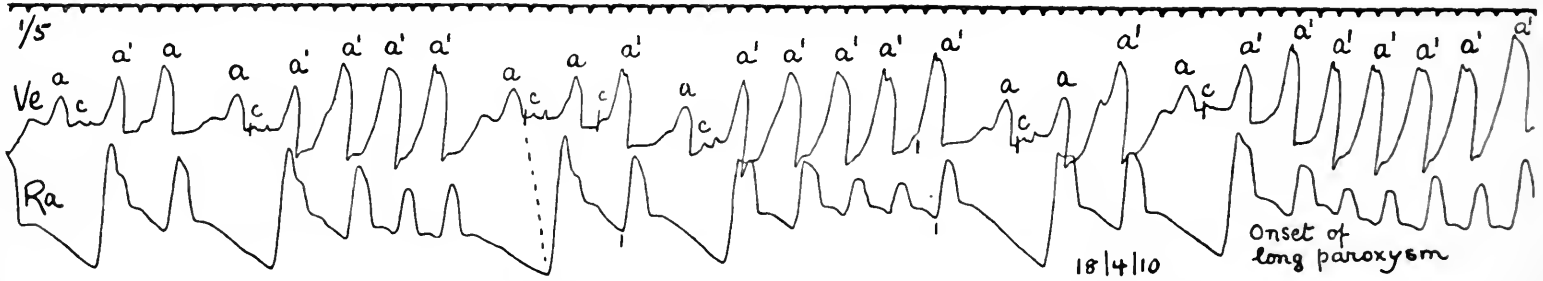

Fig. 4 is a continuation of the preceding figure, and shows the irregularity which follows the end of a paroxysm, as a result of interruption of the normal sequence by beats of similar form to those of the paroxysms themselves. At the end of the curve a fresh and prolonged paroxysm commences.

And this explanation is fully justified by a detailed examination of the curve. The height of the new wave exceeds that of the normal *a* waves, but each is accompanied by a ventricular systole. The new waves vary also in their relationships to the radial beats, in itself a conclusive argument against their ventricular origin; further, the closer the coincidence with the ventricular contraction the higher is the resultant wave. The conclusion that the new waves are of auricular origin is beyond question.

The interpretation of this curve and the continuation of it (Fig. 4) is fully borne out by the succeeding tracings, in which single interruptions of the slow rhythm are seen. Examine Fig. 5 and 6. It may be said that high waves also occur as accompaniments of beats following long pauses. But there is good reason for this variation: it is due in these instances, as in those previously discussed, to synchronous auricular and ventricular contraction; in the last instances the ventricle escapes and beats are present which belong to an ideo-ventricular rhythm. Where a comparison with electric curves provides an easy solution of the mechanism (Fig. 10, 11 and 12), positive evidence of simultaneous contraction is forthcoming.

The electric curves (Fig. 10, 11 and 12) are examples of a large number of photographs, and are selected to illustrate special points connected with the interpretation of the mechanism as presented by Fig. 5 and 6. The venous and electric curves referred to were taken within half an hour of each other. In the radial curves of Fig. 5 and 6 the beats occur in groups of two and three. Similar groups are shown in the electric curves. In Fig. 10 two complete groups of three ventricular cycles are shown. Each heart cycle is accompanied by P, R and T variations. In each group the P-R interval increases from 0·6—1·7 sec., and the last beat, which is of anomalous form, is succeeded by a long pause. The relation of the P and R variations is similar to that of the *a* and *c* waves in Fig. 6. The shortening of the P-R interval after a pause, to $\frac{0·8}{5}$ sec., is conspicuous. In other curves it is still greater, and the interval diminishes until P and R partially coincide (Fig. 11), or until the auricular complex is completely buried in the ventricular complex (Fig. 12). As all stages of shortening are present, it is impossible in certain given instances to ascertain whether the ventricular beat is a response to the auricular, or whether it is generated in the ventricle. It is probably ideo-ventricular in Fig. 11. It is certainly ideo-ventricular in Fig. 12; the last beat in the curve consists of a superimposition of auricular and ventricular complexes. Thus the coincidence of As and Vs, suspected after an examination of the venous curves, is demonstrable.

The paroxysmal cycles are known, from the consideration of venous and electric tracings, to consist of simultaneous auricular and ventricular systoles; but this is not obvious in the electric curves alone (Fig. 9). Neither can the auricular contractions, which are recognised as falling with the

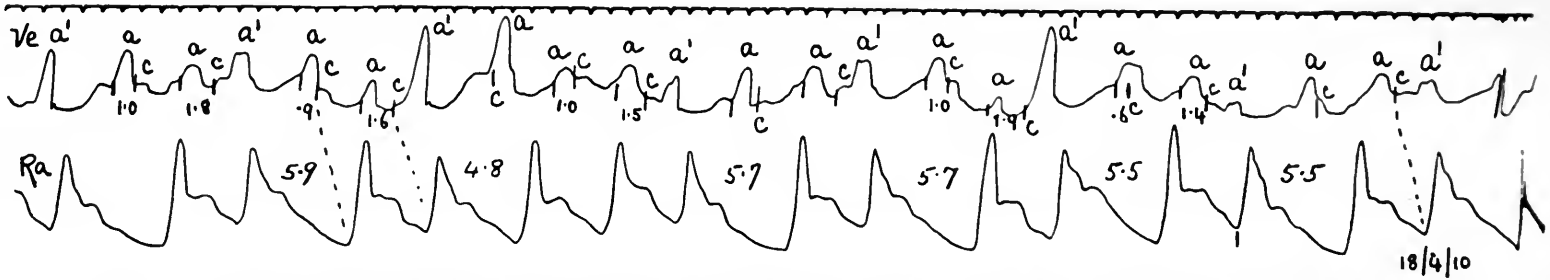

Fig. 5. A curve taken at the cessation of a paroxysm shown at the end of Fig. 4. The degree of irregularity is relatively small. There are interruptions of the normal sequence by beats of paroxysmal type. The examination of the *a*-*c* intervals shows conductivity changes, which are more fully described in the text. At one point in the curve an escaped ventricular contraction is seen.

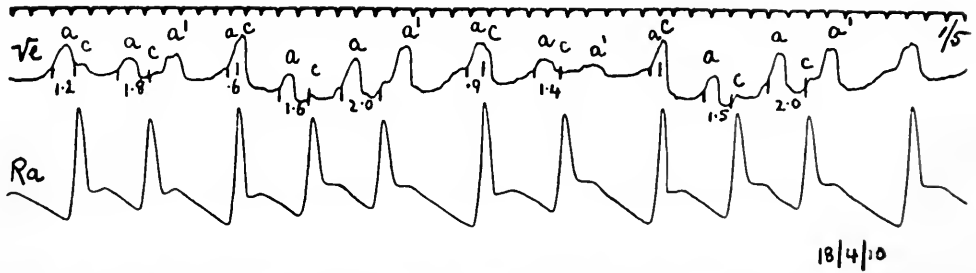

Fig. 6. A curve of the same sort, in which single premature contractions interrupt the auricular sequence at less frequent intervals. Evidences of the escape of the ventricle and of conductivity changes are clear in the venous curve.

last beats of the groups (Fig. 5 and 6 and Fig. 10, 11 and 12), be identified in the electric curves. The reason of the failure of the premature P variations (single or paroxysmal) in the electric curves is clear. The auricular contractions take an abnormal course in the auricle; that is to say, they commence at a point in the musculature other than the pacemaker. Under these circumstances the electric changes which accompany such contractions are anomalous, and in the present instance the form of the curve to which they give rise is unknown. That auricular contractions originating in an abnormal fashion give rise to abnormal electric variations is known from a study of the experimental facts in regard to them.[3] In this case the abnormal Ps are probably of a type approaching the isoelectric position. It was hoped that a clearer appreciation of the form of anomalous Ps would be obtained by comparing the cycles in various leads, and with slightly divergent heart rates (Fig. 9, *IV* and *VII*), but the analysis has been found impracticable. We remain satisfied that the contractions of auricle and ventricle are simultaneous, although the identification of the former is impossible in the electric curves.*

Returning to the mechanism of the paroxysms, and knowing that each cycle consists of a synchronous As and Vs, there are two alternative interpretations of the events open to us. It may be supposed that the auricle and ventricle contract together in response to a single stimulus originating between them, or that each ventricular contraction is a response to the auricular systole which coincides with the preceding ventricular contraction. Either interpretation meets the facts of the case in so far as we have yet considered them. The instants at which As and Vs fall in the venous curves are fully determinable, and we have to consider the functional relationships of the separate beats.

For purposes of illustration I have diagrammatised the two interpretations of the first short paroxysms of Fig. 3 (in Fig. 7, *1* and *2*) and the first six ventricular cycles of Fig. 6 (in Fig. 7, *3* and *4*).

(1) Dealing with the first interpretation, namely simultaneous As and Vs, as a result of As falling back upon Vs (Fig. 7, *1* and *3*), it will be obvious that if this explanation is adopted, it necessitates the assumption that all single premature auricular contractions are blocked. But it likewise involves the unreasonable assumption that the last beat of each paroxysm, be it short or long, is blocked too.

(2) Adopting the second interpretation (Fig. 7, *2* and *4*), namely simultaneous contraction of A and V as a result of a single impulse formed between them, we have to allow that the auricular contraction of the normal sequence directly preceding the onset of the paroxysm is blocked, or if this is not blocked, then the first impulse starting the paroxysmal contraction gives a response in the auricle alone.

* An instance in which venous curves show what electric curves will not demonstrate.

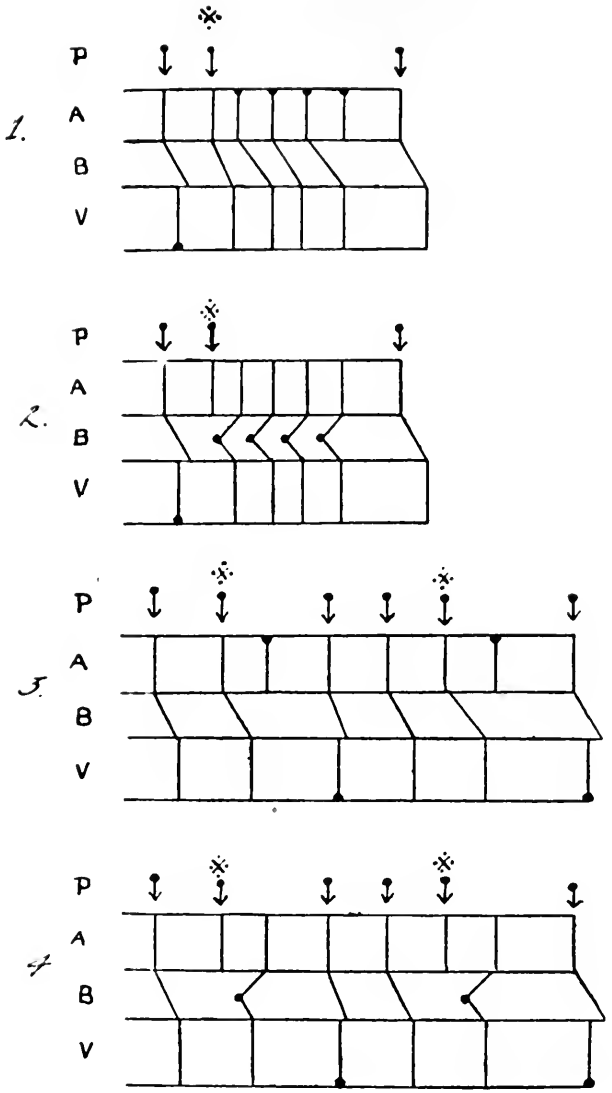

Fig. 7. Four diagrams illustrating the possible interpretations of mechanism in two portions of the preceding curves. Fig. 7, *1* and *2* are alternative explanations of the first short paroxysm of Fig. 3. Fig. 7, *3* and *4* are alternative and parallel explanations of the first five beats of Fig. 6. The arrows drawn above each diagram represent impulses which descend from the pacemaker and give rise to auricular contractions. A represents the auricle, B represents the junctional tissues, and V represents ventricle. The black dots are intended to represent the point at which the impulses may be supposed to arise.

The facts will not permit a positive decision in one way or the other, but on the whole they are in favour of the second explanation. No appreciable change has been found in the relationship of As to Vs during the paroxysms with considerable divergence of rate, and no ventricular beat has ever been dropped at such times. Finally, we can only conclude that we are dealing with a supraventricular form of paroxysmal tachycardia, in which the contraction of auricle and ventricle is simultaneous, and that of two propositions (delay in conduction from A to V, and impulse formation between A and V), which might be adopted in explanation of the phenomena, the second appears to be the more reasonable.

Certain features of the curves remain for brief discussion or mention.

(1) The last ventricular complex of each separate group in Fig. 10, 11 and 12 is of anomalous form. T is partially inverted. Such beats are of a form transitional between the normal complexes on the one hand and the paroxysmal complexes on the other. The alterations in a ventricular complex resulting from a premature auricular contraction have been described in detail in an article to the last number of this *Journal*,[3] but evidence was produced which showed that the prematurity of the auricular contraction is not the sole cause of the alteration in the ventricular curve. It appears to associate itself with two phenomena; the first of which is the close proximity of the premature beat and that which precedes it (brought about in the present instance by variation in the lengths of the As-Vs intervals), and the second of which is the presence of demonstrable changes of conductivity in some portion of the heart muscle. Fig. 12, taken at a fast rate, is given that the comparison between the single anomalous complex and the beats of the paroxysmal type may be more readily compared. There is no reason to suppose from the general conformity of the single anomalous beats that they have arisen other than in response to the preceding auricular contraction.

(2) The single atypical beats of Fig. 10, 11 and 12 are of interest in showing a gradual decline of T. It is some while before the curve becomes horizontal or isoelectric. The usual experience in dealing with premature complexes is to find the total length of an individual ventricular complex equal, within small errors of measurement, to the complex of the normal rhythm.[4] In this instance there is a marked divergence from the customary findings, but the cause of the extension of T is quite obscure. It cannot be assigned to activity of the auricle; the prolongation is too great. A similar condition is found in the paroxysms themselves. In the leads from right arm and left leg (Fig. 9, *IV* and *VII*), no portion of the curve is isoelectric for any length of time. Here, again, the meaning of the phenomenon is not ascertainable.

The ventricular form of venous pulse in association with retrograde heart-beats.

In the introductory paragraphs of the present communication it was stated that the ventricular form of venous pulse is to be anticipated when a paroxysm of tachycardia, originating in the ventricle, dominates the rhythm of the whole heart. I have met with two clinical instances in which ventricular paroxysms were present, but they were of brief duration and the venous curves were not obtained.

A polygraphic curve taken from an anæsthetised dog, and showing a complete paroxysm of ventricular tachycardia is shown in Fig. 8. The paroxysm was induced by interrupted stimulation of the ventricle; the chest wall was closed at the time. The normal sequence of events is shown in the opening cycles of the curve. The first interruption consists of a single premature ventricular beat, which fails to affect the femoral curve. One cycle of normal sequence follows, and a ventricular paroxysm of 15 beats succeeds it. The first four auricular peaks, which occur after the onset of the paroxysm, are placed at regular intervals, and at the expected points in continuation of the preceding auricular rhythm. They vary in height according to the stage of ventricular systole at which they fall, being taller when coinciding with the earlier phases of ventricular contraction. The venous curve then assumes a perfectly regular appearance. The auricle and ventricle are now contracting together and at constant time relationships to each other. In other words, the ventricular rhythm has become regularly retrograde. The representative of auricular contraction is seen rising from the plateau in each cycle of the venous curve. That this peak is in reality the result of auricular contraction is known by comparing the two cycles marked x, x. In the venous curve they show a close resemblance to each other, differing only in the very slightly earlier appearance of *a* in the first of the two cycles considered. Its appearance in the first cycle marked x is not due to retrogression, but it is due to the expected response of the auricle to sinus impulse formation. On the other hand, it appears prematurely in the second cycle, and represents the first retrograde auricular contraction. The venous curve during the reversed mechanism, which is maintained from this point onwards, is of the ventricular form.

Summary.

A case of paroxysmal tachycardia is described in which the ventricular form of venous pulse was present, as a result of simultaneous contraction of auricle and ventricle.

The ventricular form of venous pulse is also found (experimentally) when reversed heart rhythm is present.

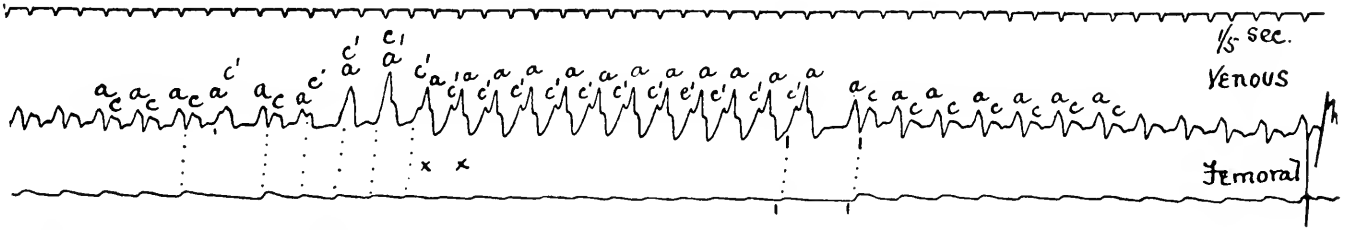

Fig. 8. A polygraphic curve from a dog, showing the form of the venous pulse when the rhythm of the heart is reversed and auricle is responding to ventricle.

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Fig. 9. $\times \frac{1}{2}$ linear.

I, 15-4-10. An electrocardiogram taken during the interval between two paroxysms. The P-R interval is 0·16 sec.. P is exaggerated, and in its outlines resembles auricular complexes obtained in other cases of mitral stenosis. The lead is from the right arm and left leg.

II, 3-5-10. The same as *I*; the lead is from the left arm and the left leg.

III, 3-5-10. The same as *I* and *II*; lead from right arm and left arm.

IV and *V*, 20-4-10, and *VI*, 24-4-10. Three curves taken during paroxysms with same leads as in *I*, *II*, and *III* respectively.

VII, 24-4-10. Lead from the right arm and left leg taken during a paroxysm and for comparison with Fig. 9, *IV*, in which the heart-beat is at a somewhat slower rate.

VIII, 20-4-10. Taken during a paroxysm, the lead being from the sternum at the junction of the second rib and from the apex.

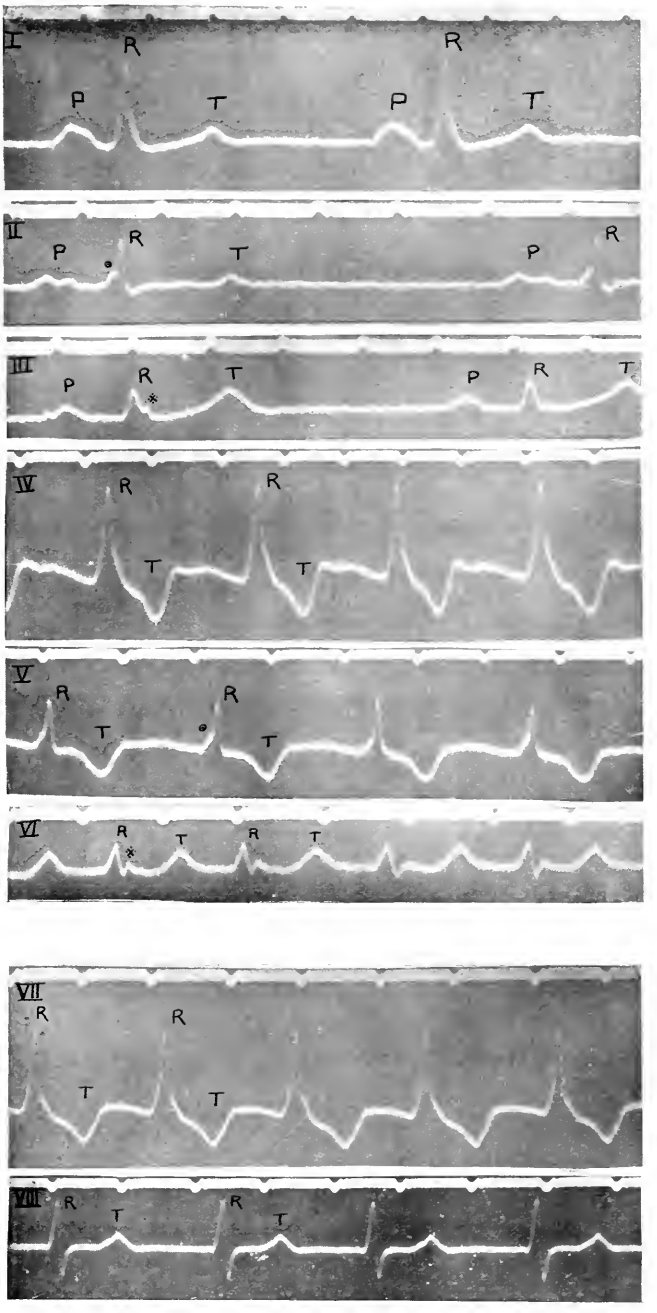
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Fig. 9.

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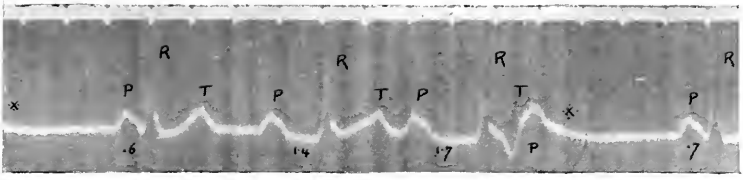

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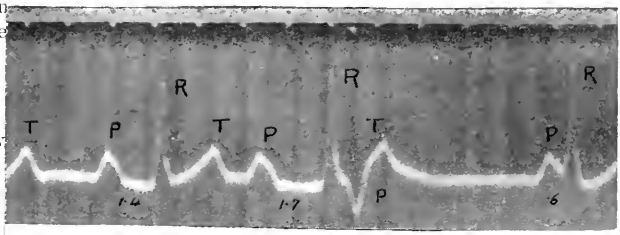

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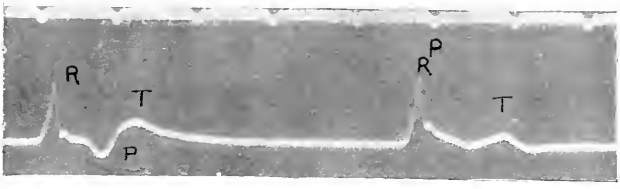

Fig. 12.

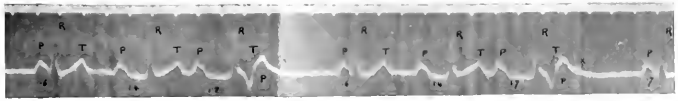

Fig. 10.

Fig. 10. 18 4 10. ½ linear. Electrocardiogram from right arm and left leg taken si after the cessation of the long paroxysms, shown in the text, Fig. 3 and 4. The t clearly shows the correctness of the interpretation of Fig. 5 and 6; it shows two be anomalous form at the termination of two groups of three beats. The P-R interval a notable increase during the progress of each separate group of beats.

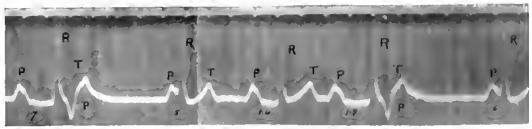

Fig. 11.

Fig. 11. 18 4 10. ½ linear. A similar curve from right arm and left leg taken at the time and showing a remarkable shortening of the P-R interval at the commencem each group of beats. The interval is too short to permit the supposition of ventri response to an auricular impulse.

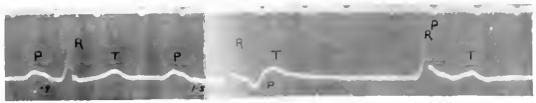

Fig. 12.

Fig. 12. 18 4 10. ½ linear. A similar curve taken from right arm and left leg and higher speed for the purpose of comparison with the preceding curves. The third in the strip clearly demonstrates the escape of the ventricle and simultaneous contract of auricle and ventricle.

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THE REACTION OF THE HEART TO DIGITALIS WHEN THE AURICLE IS FIBRILLATING.*

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IN a communication published in *Heart* in March of this year[1] it was shown that the completely irregular pulse,† which is so frequently encountered in clinical work, and which is peculiarly associated with advanced mitral stenosis and arterio-sclerosis, is the result of a condition well known to experimentalists—namely, fibrillation of the auricle.

I do not propose to reiterate at the present time the detailed evidence upon which this conclusion rests, but content myself by stating that the conclusion is in absolute accord with all the known characters of the experimental and clinical conditions. It may be stated that a similar irregularity of the heart occurs in horses, and since the publication of my full paper I have had a further opportunity of examining the heart of such an animal beating *in situ*. The auricle was fibrillating.

When the heart is inspected in an animal in which the auricle (speaking of right and left auricles as a whole) is fibrillating, this chamber is found to be in a state of continued diastole. No co-ordinate contraction of its walls interrupts its condition of distension, but careful examination discovers a flickering or tremulous state of the musculature. The muscle seems to be alive with the movement, yet no given point shows any appreciable excursion.

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* A paper read in the Section of Pharmacology at the annual meeting of the British Medical Association, July, 1910.

† Or "pulsus irregularis perpetuus." The rhythm of the heart has passed under the terms "arrhythmia perpetua," "nodal rhythm," and "chronic arrhythmia."

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The interpretation of the phenomena witnessed is a simple one. In a normally beating heart the auricle responds to rhythmic impulses generated in the neighbourhood of its junction with the superior vena cava,[2] and it contracts as a whole, expelling its contents into the ventricle. The movement of the auricle is a rapid one, and there is shortening of the muscle in every direction. It is supposed that in the fibrillatory state this normal impulse formation is in abeyance, and that in its stead numerous and small areas of the hyper-irritable musculature are building up independent and pathological impulses; it is further supposed that the resulting waves of contraction, pro-

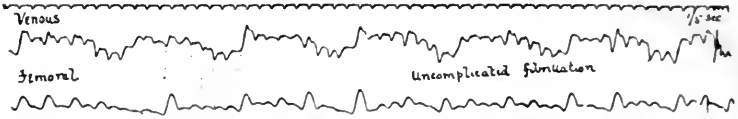


Fig. 1.—Venous and femoral curves from a dog during a period of auricular fibrillation. The venous curve is ventricular in form. The pulse is completely irregular.

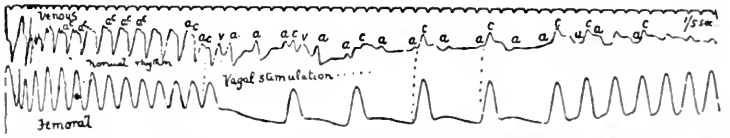


Fig. 2.—Venous and femoral curves showing the effect of vagus stimulation. With the stimulation 2:1 heart-block appears.

pagated from each and all of the new impulse centres, meet each other in the walls of the auricle without travelling far, and that as a consequence the whole of the contractile substance of this chamber is thrown into delirium. There is no co-ordinate contraction, meaning by co ordinate contraction universal contraction of the fibres in a definite order and eventually together. There is a condition of asystole.

Now, while the auricle is in this state the *individual* ventricular systoles are co-ordinate; but the chamber beats in a rapid and highly irregular fashion. Thus,

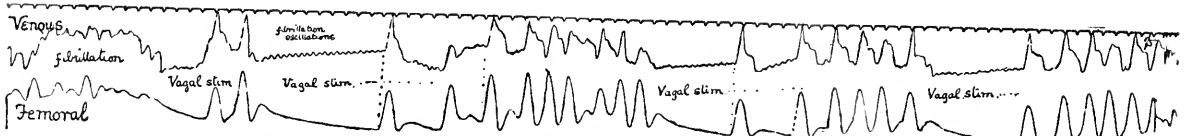


Fig. 3.—Venous and femoral curves from a dog. The auricle is fibrillating throughout, and the venous pulse is of the ventricular form. When the vagus is stimulated the ventricle ceases to beat, but the auricle continues to fibrillate, and leaves its impress on the venous curve in the form of small and rapid oscillations.

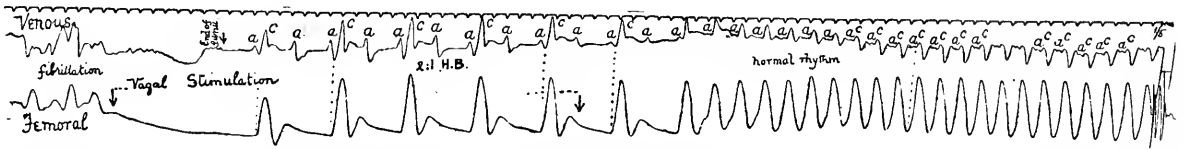


Fig. 4.—The end of a period of auricular fibrillation. Its termination results from vagus stimulation. The oscillations cease where the fibrillation ends, and from this point co-ordinate auricular contractions are represented. A condition of 2:1 heart-block is present. To show that the ventricular slowing while the auricle is fibrillating is the outcome of heart-block.

while each contraction of the ventricle is of a similar nature to a normal systole, the sequence of contraction presents no rhythm, but has a completely disordered character. In explanation of this gross irregularity in the ventricle it is supposed that occasional impulses escape in a haphazard fashion from the turmoil in the auricle, and that, like normal impulses, they are transmitted across the junctional tissues, the auriculo-ventricular bundle and its arborizations, to the ventricle.

It is upon a heart whose mechanism is disturbed in this way that digitalis exerts its most conspicuous action. Given in full doses it frequently produces a marked retardation of the ventricular rate. In inquiring into the cause of the retardation it is essential, first, that the condition of the auricle should be remembered; and, secondly, that we examine the known ways in which ventricular slowing may be brought about when the auricle is fibrillating. In the experimental heart, when fibrillation of the auricle is present, retardation of the ventricular rate follows certain definite procedures. It results from stimulation of the vagus nerve (Fig. 3), and it has been suggested by Professor Cushny[3] that such slowing is the outcome of an increased obstruction to the passage of impulses across the auriculo-ventricular junction; for it is known that the conductive functions of the junctional tissues are markedly depressed by inhibitory impulses, and that heart-block in an otherwise normal heart is a ready consequence of vagus excitation (Fig 2).

The curve now demonstrated (Fig. 4) strongly supports this view. It shows simultaneous venous and arterial curves from a dog in which the auricle is fibrillating. Accompanying stimulation of the vagus the ventricular rate is diminished, while the fibrillation, identified by the small and rapid oscillations in the venous curve, proceeds. A few seconds later the fibrillation terminates, and the normal and co-ordinate auricular contractions are re-established. When these rhythmic contractions of the auricle appear, it is seen that only one in two transmits an impulse to the ventricle and excites a response. The slowing of the ventricle at this stage is the result of heart-block; the presumption is that the slowing previously manifested was of similar origin.

It has been shown by Fredericq[4] that the ventricle beats slowly and regularly when the auriculo ventricular

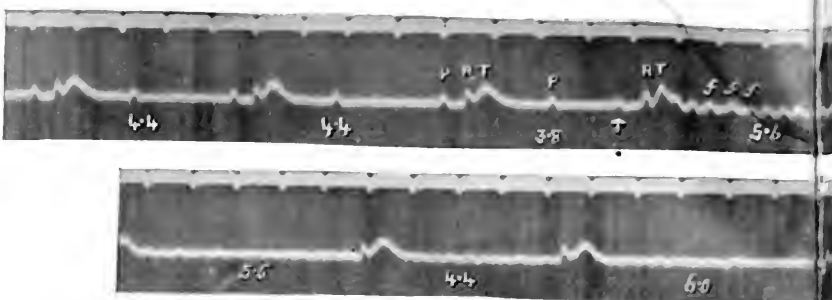


Fig 5.—A continuous electro-cardiographic curve taken from a cat during a period of as
variations P: the ventricle is represented by the variations R and T At the point marked b
immediately changes. The normal auricular waves are replaced by the fibrillation waves (*fff*)
irregular. The curve is continued, and shows the breakback from fibrillation + heart-block t
more faradized and fibrillation ensues. The curves show the effect of heart-block in hinderin

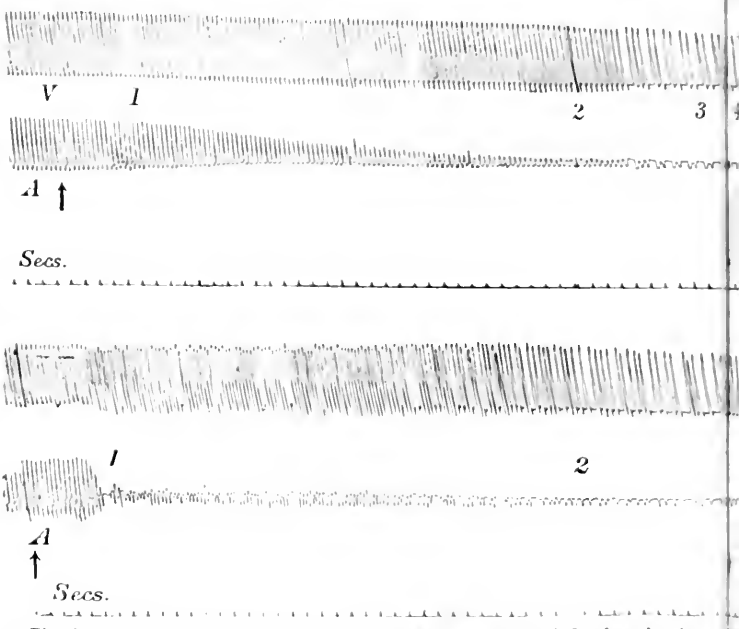
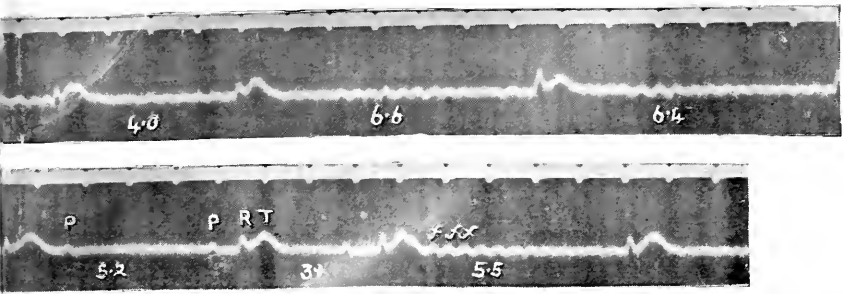
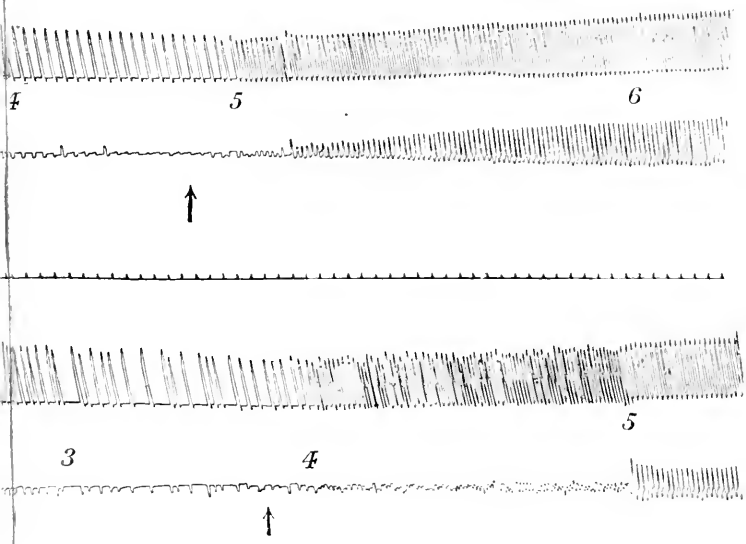


Fig. 6.—Two curves taken from a cat during successive periods of asphyxia.
begin and end where the arrows are placed. The first curve is of uncomplicated
(from the points 1 to 5) the auricle was faradized and sent into fibrillation.
asphyxia. Up to this point the excursion of the auricle has greatly decreased, a
alone. At 5 the auricular contractions are again seen, and once more increase
block is seen. At the point marked 5, shortly after the onset of respiration, the he
auricle begins. It is accompanied by an increase of ventricular rate and by irre
marked 2 the rate of the ventricle *gradually* decreases up to a point lying betwee
increases Again, at the point marked 5 fibrillation ceases, and the normal seq
upon the transmission of impulses from auricle to ventricle during co-ordinate act
earlier when the auricle is fibrillating; in the one case the curve shows an abrupt



xia The curve starts when 2:1 heart-block is established; the auricle is represented by the e arrow in the upper curve the auricle was faradized, and fibrillation ensued. The type of curve At the same time, though the ventricle shows no marked change of rate, its rhythm becomes chythm in which 2:1 heart-block is present. At the end of the lower curve the auricle is once e transmission of impulses from a fibrillating auricle.



v[yocardiogram of ventricle; A=myocardiogram of auricle. The periods of asphyxia a yxia. The second curve is of a similar asphyxial period, during the whole of which At point lying between 2 and 3 in the upper curve heart-block occurs as the result of the an rom this point onwards the movements of the curve represent tug from the ventricle se xcursion. The heart-block starts with an occasional dropped beat. At 4, 2:1 heart- he block disappears. In the second curve, and at the point marked 1, fibrillation of the m arity of the ventricle, seen in the outlines of the ventricular curve. From the point re and 4. Just before point 4 respiration starts once more, and the rate of the ventricle se ce of heart contraction is resumed. The two curves show the effect of heart-block ac and fibrillation of the auricle. The obstruction to the passage of impulses shows ri ng of the ventricle; in the other case retardation is more gradual

bundle is transected, and while the auricle is fibrillating—a fact which demonstrates that all auricular impulses to it are impeded by such a procedure. As a consequence the ventricle assumes its own spontaneous slow and regular rhythm. Partial heart-block is readily induced by asphyxia, and, in conjunction with Dr. Mathison, I have utilized this fact to show that when a condition of heart-block is present, the production of auricular fibrillation, while disturbing the regularity of the ventricular contractions, fails to bring about the marked increase of rate which usually accompanies its onset in the normal animal. It may be similarly shown that when the auricle is fibrillating the production of partial heart-block reduces the rate of the ventricular responses (Figs. 5 and 6).

The clinical condition, auricular fibrillation, has been seen in association with heart-block of several grades; with partial heart-block in the curves of Dr. G. A. Gibson,[5] by Dr. Mackenzie,[6] and myself; in all these cases the ventricular rate was slow; and a case of auricular fibrillation has been recently reported in which complete heart-block in an epileptic and syphilitic subject was probably present.[7] In this case the ventricle beat regularly at a rate of approximately 30 per minute.

We see, therefore, that the known ways in which the ventricular action may be retarded, whether the fibrillation is clinical or experimental, are of one type; in all instances heart-block is either probable or proved. What more natural than to suspect that digitalis acts in a similar manner when it produces ventricular slowing in the clinical condition? For digitalis has been found to induce heart-block experimentally,[8] and clinically a similar action has been described by Mackenzie,[9] and has been fully substantiated by a number of more recent workers.

The case for which I plead—that digitalis slowing is a result of heart-block when the auricle is fibrillating—is very materially strengthened when the following facts are considered: The type of case in which, with the normal or co-ordinate contraction of the auricle present, heart-block is readily provoked by digitalis administration, is the advanced rheumatic heart, and *a fortiori* the heart affected by mitral stenosis. It is a striking fact that of all cases

of clinical auricular fibrillation, those which are of rheumatic origin, and *a fortiori* those affected by mitral stenosis, show the characteristic slowing of digitalis to most advantage. This is the type of case in which digitalis acts in so magic a fashion, and in which the rate of the ventricle is set by the dosage employed; it is the type of case in which the ventricular rhythm may be sometimes reduced to regularity, and in which the rate may be reduced to that consistent with a true ventricular rhythm.

On the other hand, there is the type of patient in whom no reaction ensues upon the exhibition of the drug. Now Mackenzie has shown that digitalis produces heart-block in those patients in whom a previous defect of conduction exists. The proposition I put to you is a parallel one, namely, that the ventricle is retarded in auricular fibrillation by digitalis when there is a pre-existing damage of the junctional tissues, a damage which is frequently demonstrable in cases of rheumatic heart affection.*

The complete evidence in support of this proposition will require time for its collection. We require observations upon patients in the early stages of the affection. It is requisite that it be demonstrated that a large proportion of the cases which react to digitalis had a deficiency of auriculo ventricular conduction *before* the onset of fibrillation. I can offer the facts in regard to three cases[10] only at the present time. In these three cases the heart-rhythm was observed before the onset of fibrillation, or during the intervals of rest between attacks. The cases were thoroughly tested with digitalis during the stage of fibrillation. Two cases, in which no previous defect of conduction could be demonstrated, failed to show a trace of reaction to the drug. The third case in which deficiency of conduction was clearly established reacted repeatedly and in the most typical manner.

The view suggested, therefore, is that the ventricular rate is retarded in clinical auricular fibrillation by the action of digitalis upon the junctional tissues, the functions

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* The view that digitalis acts by the production of heart-block was originally put forward in the BRITISH MEDICAL JOURNAL of November 27th, 1909, and was more fully considered in *Heart*, 1909-10, 1, 349.

of which are already in a depressed state; and this view is put forward, together with an indication of the direction from which the evidence will come, which, if favourable, should convert what may be now regarded as a proposition into a well-established conclusion.

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Journal Physiology, Vol. XLI.
[*From the Proceedings of the Physiological Society*, Nov. 19, 1910.]

The pacemaker of the mammalian heart as ascertained by electrocardiographic curves.

By THOMAS LEWIS[1].

(*University College Hospital Medical School.*)

In a paper published in the July number of *Heart*, an account was given of certain observations on the dog's heart. Electrocardiograms were taken with the string galvanometer from the upper and left lower extremities, and the auricular portions of the normal curves were compared with the auricular portions of curves accompanying beats of the heart excited from various areas of the auricular musculature. It is known that the course of the contraction wave in muscle controls the type of electric curve yielded by such contraction. The supposition was, therefore, that beats of the heart excited from various portions of the auricular musculature would show differences in the auricular portions of the curves, and that excitation of the area from which normal heart-beats started, would yield curves which were duplicates of the normal curves.

The actual experience, in a series of thirteen experiments, was that duplicate curves are obtainable from an area enclosing the upper half or two-thirds of the sulcus terminalis, and a small surrounding area. It is in this area that the sino-auricular node of Keith and Flack lies. A closer examination of the site of the pacemaker by this method was found to be impossible, and observations by another method were undertaken in conjunction with the Doctors Oppenheimer.

We used non-polarisable electrodes of the type described by Gotch, and employed in leading directly from the musculature of the heart. The object of these experiments was the determination of the point on the surface of the right auricle, which becomes primarily electro-negative at the contraction of the auricle. In a series of experiments, it was found that the point of initial electro-negativity could be identified within very narrow limits. It lies immediately in the vicinity of the cavo-appendicular angle, that is to say, at the cephalic extremity of the sulcus terminalis.

A number of points on the exposed surface of the auricle were tested against this point, with uniform results in a series of nine experiments. In seven of the experiments, the points from which leads were taken were marked while the heart lay *in situ* (for subsequent

[1] Working under the tenure of a Beit Memorial Research Fellowship.

identification) and the tissue of the sulcus terminalis and the portion of the auricle bordering upon it were excised and cut into blocks, each of which surrounded one of the points from which a lead had been taken. The blocks of tissue were cut serially from above downwards, and the relationship of the specialised tissue (sino-auricular node) to the point of primary electro-negativity was ascertained.

It was found in all cases without exception that the point of primary electro-negativity lay immediately over the cephalic end of the sino-auricular node, which in the dog occupies the upper half or two-thirds of the sulcus terminalis.

As a general rule, an enlargement of the node was found at this point, and in the seven hearts examined the tissue of this end appeared to have a more specialised character as compared with that which constituted the remainder of the node.

Thus, the electrical observations lead us to a conclusion which in every way conforms to anatomical findings. There is, at the cephalic end of the sulcus terminalis, a specialised mass of tissue, richly innervated. At the same point, the musculature exhibits certain definite electrical phenomena which lead to the belief that the heart-beat originates in its immediate neighbourhood.

The observations, of which an outline is now given, will be fully reported in the November number of *Heart*, 1910.

[*Reprinted from the* Proceedings of the Royal Society of Medicine, *December*, 1910.]

The Influence of Diet upon the Formation and Healing of Acute Ulcer of the Stomach.

By Charles Bolton.

The present research is one of a series which was initiated in order to inquire into the exact part played by the gastric juice in the production and healing of acute gastric ulcer. For many years the hypothesis has been prevalent that the gastric juice plays an important rôle in the pathology of gastric ulcer, mainly because ulcers having the characters of those found in the stomach are almost entirely limited to the parts of the alimentary canal which are directly exposed to the action of the gastric juice. Many experiments indirectly bearing upon this problem have been performed in order to substantiate this hypothesis, but, it must be confessed, without much success. I have no intention in this short communication of discussing the relative merits of these experiments, because I have already referred to most of them in various other papers, and because they have no particular bearing upon the subject of this discourse. In all my experiments acute gastric ulcers have been produced in animals by the injection of gastrotoxic serum, the preparation of which I was able to demonstrate some years ago [1]. By means of this method of producing gastric ulcer I have arrived at the following definite conclusions, which have been already published in various papers :—

(1) That acute ulcer fails to appear if the gastric juice be put out of action, although the animal may die from the effects of the poison.

(2) That the ulceration produced in the presence of hyperacid gastric juice is much more extensive than that produced in a stomach secreting juice of the normal acidity [2].

(3) That the gastric juice is able to attack the gastric cells and produce an ulcer, although the cells are not actually killed by the poison. It is merely necessary to damage the cells to some extent.

(4) That hydrochloric acid of the various strengths found in the condition of hyperacidity in the human subject is able to act as a poison for the gastric cells.

(5) That acute gastric ulcer heals equally well, whether the gastric juice be increased or diminished in acidity to the extent usually found in man, provided that the stomach empties itself in the normal time [3].

(6) That acute ulcer is more easily produced in the digesting than in the resting stomach, and that in the former case it is much more extensive in character.

(7) That undue retention of food in the stomach delays the healing of acute ulcer for at least twice the normal time, because the prolonged action of the gastric juice irritates the base of the ulcer, and may cause necrosis of the granulation tissue in the early stages and excessive formation of fibrous tissue in the later stages. The growth of the new mucous membrane over the base of the ulcer is thus delayed, and there is produced more inflammatory thickening than usually occurs in the condition of normal healing [4].

Since motor insufficiency of the stomach prolongs the period of healing of an ulcer, it follows that food which is retained for a considerable time in the stomach, and which excites a copious secretion of gastric juice, should be more unfavourable to the healing of ulcer than food which leaves the stomach rapidly and excites only a moderate flow of gastric juice. This is a question of great importance to the clinician, as I think most physicians will agree that rectal feeding is inadvisable in any case in which it can be avoided, so that it is necessary to have the question definitely settled with regard to what diet is the most suitable for a case of gastric ulcer. In all the present experiments cats were used. The ulcer was in each case produced on the anterior wall of the stomach midway between the cardiac and pyloric orifices by the local injection of gastrotoxic serum, obtained by immunizing the goat with the gastric cells of the cat, as described in a former paper [5]. The two diets chosen were meat and milk respectively. After a meal of 100 grm. to 120 grm. of meat, the cat's stomach is usually not empty till a period of about twelve hours has elapsed, whilst after a

meal of 6 oz. of milk it is empty in three hours. The stomach of a 3,000-grm. cat will hold when fully distended a little over half a pint, but the animal will only drink about 6 oz. at once. There is the mechanical irritation of the meat also to be taken into account; but perhaps this is not of so much importance, because small clots are formed in the milk which will act in a similar manner. It was first demonstrated by Griffini and Vassale [7] that after removal of a portion of mucous membrane by the knife the new mucous membrane was regenerated by proliferation of the glandular epithelium at the edge of the lesion, the cells growing over the raw surface, which they cover in a single layer. The glands are subsequently developed from this single layer of cells.

In my experiments on motor insufficiency I found that the delay in healing occurred in the early stages before the single layer of cells had developed, but that when once the base of the ulcer was covered with epithelium the regeneration of the mucous membrane was chiefly a question of time, but was also to some extent dependent upon the density of the fibrous base of the ulcer. From the clinical point of view, therefore, the important point in promoting the healing of ulcer is to exercise special care in the early stages of the healing so that the single layer of cells covers the base of the ulcer as rapidly as possible, and when once that is accomplished the chief difficulty is over. I have observed the healing of acute ulcer in twenty-six cats up to the stage at which the base of the ulcer is covered with a single layer of epithelial cells, because, for the purposes of my inquiry, it was sufficient to observe the healing up to this stage. Thirteen cats were placed on a meat diet and thirteen on milk. The animals were killed at various stages, and the ulcers of twenty of these animals examined microscopically. It was not necessary to examine the remaining six with the microscope, because they were quite in an early state and the condition obvious to the naked eye. The exact time of healing, of course, depends upon the size of the ulcer. The size of the ulcer varies in proportion to the strength of the serum, which in its turn depends upon the stage of immunization which the goat has reached. In the present instance all the ulcers were produced by injection of the same dose of serum obtained from a goat at the same time, so that all the ulcers were of the same size. The serum which is injected so as to cause a local œdema of the stomach wall soaks into the mucous membrane and other tissues. The portion of stomach wall so exposed to the action of the serum is digested by the gastric juice and converted into a slough which separates, leaving a clean ulcer.

The formation of the ulcer varies according to the condition of the contents of the stomach. When the animal is on a meat diet, so that the walls of the stomach are exposed to the prolonged action of the gastric juice, the slough is rapidly formed and has separated by the fourth day in most cases, a clean ulcer resulting. In the case of animals fed on milk, however, the period of formation of the ulcer is longer. In two of the cases the sloughs had not separated on the seventh day, and in two other animals killed on the eighth and eleventh days respectively a small slough was still adherent to the centre of the base. Out of a large number of animals fed on a meat diet in previous experiments I have never yet encountered an unseparated slough like this at so late a date. There is no doubt whatever that the condition of the stomach contents exercises a great influence upon both the formation and extension of an ulcer in whatever way it is produced, and we know that in the human being acute ulcer is initiated in several ways, but in all cases, by the action of the gastric juice, the different lesions are eventually converted into precisely the same kind of ulcer. It is by no means uncommon for a sudden hæmorrhage or perforation to occur after a meal, and this is not altogether due to the stretching and movements of the walls of the stomach, but also to digestion by the gastric juice. These experiments support the result which I gave at the beginning of this paper—namely, that an ulcer is produced more easily in the digesting than in the resting stomach. On account of the delay in the separation of the slough on a milk diet, I placed six further animals on meat for the first four days, and subsequently on milk, so that the experiments would be more strictly comparable with those in which the animals were fed on meat all the time.

The microscopical examination of a lesion on the third day shows the overlying mucous membrane completely necrosed, the tissue being shrunken and unstained, and at the junction of the dead and living tissue an infiltration with round cells, chiefly leucocytes. The muscularis mucosæ has a hyaline appearance and stains badly. The submucous and muscular coats are thickened, infiltrated with hæmorrhages, and contain much necrotic tissue having a hyaline appearance. There is commencing infiltration with cells around the edge, which are invading the dead tissue.

After the slough has separated, the base of the ulcer is formed of the remains of the muscular coat or the subperitoneal tissue infiltrated with round cells. Towards the end of the second week the deeper layers of the base have become fibrous and the peritoneum is thickened, the

superficial layers being formed of granulation tissue. At the end of the third week the whole base is formed of fibrous tissue in which strands of muscular tissue can be seen. This blends with the muscular and submucous layers at the edges of the ulcer.

Until the epithelium has grown over the base the most superficial layer is formed of more vascular and cellular tissue. This is the invariable course of events in every animal fed on milk, but in those fed on meat the granulation tissue on the surface of the base and extending to various depths is liable to become necrotic. It may be only in a part of its superficial extent or in the whole of it. In this case the growth of the epithelium over the base is completely prevented, and when the whole superficial extent is involved, the epithelium has merely commenced to grow at the edge of the ulcer and the whole is completely unhealed at the end of three weeks. The size of such an ulcer is always much smaller than the original ulcer owing to contraction of the fibrous tissue in the base. This necrosis of the granulation tissue of the base of the ulcer occurred in three out of five animals which were fed on meat, and which were killed from the fourteenth to the twentieth day. The ulcers of eight animals fed on milk were examined during the same period, and in not a single case was there any sign of such necrosis.

This is the essential difference between the healing in the two cases: the granulation tissue of the base is unable to withstand the prolonged action of the gastric juice and undergoes necrosis, with the result that the healing is delayed, and the base of the ulcer becomes more dense from increased formation of fibrous tissue.

I will next consider the regeneration of the mucous membrane. As soon as the edges of the mucous membrane are separated from the slough, and all the necrotic portions of glands have been removed by the gastric juice, the cells lining the ducts and bodies of the glands, which are apparent on the raw surface, commence to proliferate and cover this surface with a single layer of at first flattened and later cubical cells. In this way the edge becomes smooth and rounded. On section this edge is composed of short, irregular glands separated by a considerable cellular stroma, the surface being covered by a layer of cubical cells, which is continued in a single layer on to the surface of the ulcer. Not uncommonly the edge has been inverted by retraction of the muscularis mucosæ, and in this case the epithelial cells are compelled to grow round the angle between this inverted edge and the base of the ulcer. This, however, appears to offer little or no obstacle to their growth. By the tenth or eleventh day in the case of milk-fed, and by the thirteenth or

fourteenth in the case of meat-fed animals, the layer of epithelial cells has extended a little way over the base of the ulcer. On the twentieth day the base of the ulcer was completely covered in four milk-fed animals, and almost completely in three others. Of the animals fed on meat, the layer of cells had only extended a short distance over the base on the fifteenth day, and of three cases examined on the twentieth day, one had a large uncovered area in the centre, and in the other two the base was completely uncovered owing to its superficial layers having undergone necrosis. The earliest time at which I have seen primitive glands develop is the tenth to the fifteenth day. They appear at first as little pouches invaginated from the layer of cubical cells.

These results, therefore, confirm those of my experiments dealing with motor insufficiency, and show that the delay in healing in that condition is merely an exaggeration of that which occurs under normal circumstances, when a diet is administered which remains for a long period of time in the stomach, the fault being in both cases in the base of the ulcer rather than in the overgrowing epithelium.

The conclusions to be drawn from these experiments are as follows:—

(1) The theory with regard to the part played by gastric juice in the production of gastric ulcer receives further confirmation, because ulceration is the more rapidly produced in proportion as the gastric juice is allowed a longer period of contact with the wall of the stomach.

(2) The epithelium grows over the base of an ulcer more rapidly when the animal is given a milk diet than when it is given a meat diet. In the case of a milk diet the base of a moderately-sized ulcer is usually completely covered up by the twentieth day, whilst in the case of a meat diet the same sized ulcer would in most cases be uncovered in the centre at that time.

(3) Frequently in the case of meat-fed animals the ulcer is completely uncovered on the twentieth day, the granulation tissue of the base of the ulcer having become necrotic. Such an ulcer may be only one-sixth of the size of the original ulcer owing to the contraction of the fibrous tissue in the base, although healing has only commenced at the edge.

(4) In the treatment of a case of ulcer of the stomach, the following principles should be observed: (*a*) During the early stages of the healing of acute ulcer the patient should be given a food which does not stay long in the stomach, and which does not excite a copious flow of gastric juice. (*b*) The period of treatment in bed should be at least three weeks. (*c*) The starvation diet of the older physicians is not necessary, because

the general nutrition suffers too much, and because ulcers heal well on some diet such as the above. (*d*) In the case of acute ulcers which are extending, or chronic ulcers, healing cannot be expected to occur in three weeks, because the ulcer must first be got into a suitable condition for healing, and then, owing to its size and thickness, the healing must take some weeks longer to be completed; so that the treatment in bed is to be conducted like that of simple acute ulcer, but extended over a period at least twice as long. (*e*) Since in many cases of gastric ulcer there is hyperacidity of the gastric juice, and when the gastric juice is acting destructively, hyperacidity increases this destructive tendency, the high degree of acidity should be controlled by the administration of alkalies. This is not so necessary in acute ulcer as in the more chronic forms, because the few estimations that have been made of the gastric secretion in acute ulcer show that it is not hyperacid, and I have found experimentally that the effect of acute ulcer is to diminish the secretion in the early stages, and that the latter becomes normal as the ulcer heals [6].

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Some Investigations Dealing with the State of Aggregation of Matter.—Parts I–III.

By S. B. SCHRYVER, D.Sc., Ph.D., Chemist to the Research Institute of the Cancer Hospital.

(Communicated by Prof. E. H. Starling, M.D., F.R.S. Received August 12,—Read November 17, 1910.)

PART I.—*On the Action of Salts in Heterogeneous Systems, and on the Nature of the Globulins.*

A. GENERAL THEORY AND RESULTS.

During the course of some investigations on the action of formaldehyde on the proteins, the observation was made that this aldehyde, when added to an aqueous solution of Witte's peptone, produces a precipitate, and that the reaction could be either partially or completely inhibited by the presence of neutral salts. This phenomenon was also noticed some years ago by T. Sollman,* who offered no satisfactory explanation of the facts. The more recent investigations of Sörensen† have shown that when formaldehyde reacts with amino-acids a methyleneimino-derivative is produced, which is readily hydrolysed in the presence of water, yielding the original amino-acid and formaldehyde. The reaction is therefore a reversible one, and can be represented by the general equation

$$(NH_2)R{\cdot}COOH + HCHO \rightleftarrows (CH{:}N)R{\cdot}COOH + H_2O.$$

The amino-acid is only completely converted into the methyleneimino-derivative in the presence of a large excess of formaldehyde, and the methyleneimino-acid thus produced is, in contrast to the amino-acid from which it was formed, so strongly acid that it can be titrated with caustic alkalis in the presence of phenolphthalein as indicator. These results are an

* 'American Journal of Physiology,' 1902, vol. 7, p. 220.

† 'Biochem. Zeitsch.,' 1907, vol. 7, p. 45.

extension and application of those which had been obtained some years before by Schiff.*

It was noticed that when formaldehyde was added to Witte's peptone, and the reaction mixture was then titrated by the Sörensen method, the same amount of alkali was required for neutralisation both in the presence and absence of salts, *i.e.* whether the precipitate was formed or not. In both cases, therefore, the formaldehyde had entered into reaction with the amino-groups in the peptone. A clue to the nature of the phenomenon was afforded, however, by Schiff's observation that asparagine, when treated with formaldehyde, yields a methyleneimino-derivative, which readily undergoes polymerisation or condensation in which more than one molecule takes part, with the formation of a complex insoluble compound.† It was therefore conceivable that certain constituents of Witte's peptone react in a similar way, and the experiments recorded in the succeeding communication indicate that the precipitate is formed from the most complex polypeptide constituents of the peptone. If these be sufficiently complex as to be of colloidal nature, and to yield a solution which acts as a heterogeneous system, it is conceivable that adsorption of salts takes place on the surface of the colloidal molecules, and thus, by a kind of sterical inhibition, prevents the reaction of the large molecules with one another, to form, in the case under consideration, highly complex polymers.‡

The inhibitory action of salts on the polymerisation or condensation of the methyleneimino compounds was studied quantitatively in some detail (see succeeding paper), and found to agree very closely (with certain exceptions, which can be readily explained) with their inhibitory action on the formation of the zinc protein compounds which are produced when zinc sulphate is added in small quantities to protein solutions.§

During the course of these investigations it was also noticed that a marked parallelism existed between the inhibitory action of salts on the formation

* Liebig's 'Annalen,' 1901, vol. 319, p. 287.

† Liebig's 'Annalen,' 1899, vol. 310, p. 25.

‡ Instances of sterical hindrance of reaction by atoms or groups combined in a molecule are, of course, well-known in the chemistry of simpler organic compounds, and are dealt with in detail in text-books on stereochemistry. (*Cf.* Stewart, 'Stereochemistry,' pp. 314–443.

§ The conditions of the reaction between zinc sulphate and protein solutions are somewhat complex and have been studied by Pauli (Hofmeister's 'Beiträge zur Physiol. u. Pathol. Chem.,' 1905, vol. 6, p. 233). He found that when egg-white solution of a given strength was mixed with zinc sulphate solution of varying concentrations, two maxima of precipitation occurred. The amount of precipitate gradually increased when the concentration of the zinc salt rose from 0·001 to 0·05 normal. As the concentration increased beyond this point, the amount of precipitate formed gradually diminished until a concentration corresponding to that of a normal solution was attained. At this point

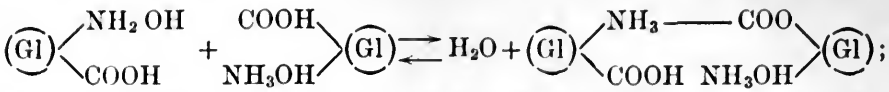
of the precipitate produced when formaldehyde is added to Witte's peptone and their capacity for dissolving the globulins, and this analogy suggested an explanation of the chemical character of this class of proteins, and of the fact that they are soluble in certain salt solutions, and insoluble in water.

From general considerations of the chemical characters of proteins and their hydrolysis products, it is conceivable that substances of this class can be either basic or acid in their nature, or that they can be truly amphoteric, and combine both acid and basic properties. As members of the basic class, which yield on hydrolysis chiefly diamino-derivatives, the protamines may be cited as examples. Other proteins of distinctly acid character are also known, in which class caseinogen and other phosphoproteins may be included, although such substances belong, strictly speaking perhaps, to the class of conjugated proteins. The investigations of Hardy on serum globulin,* and of Osborne on edestin,† have shown that the globulins have both acid and basic functions. If it be assumed that globulins contain both basic and acid groups in the molecule, and so situated stereochemically that internal neutralisation between these groups cannot take place, then it is possible that two molecules can enter into reaction with one another forming a complex according to the scheme—

no precipitate whatever was produced, and no further precipitation occurred until the concentration of the zinc salt was twice normal. The precipitate formed at the lower limits differed from that formed at the upper limits in that the former was irreversible (*i.e.* did not redissolve on diluting or concentrating the solution), whereas the latter was reversible. The precipitate formed at the lower limits is that of the zinc salt of the protein, whereas that formed at the upper limits is the ordinary protein precipitation by salts. The following is suggested as a possible explanation of this action of zinc salts on proteins. If the carboxyl groups in the protein molecule are situated so far apart that the salt of the dyad metal cannot be formed by replacement of the hydrogen from two carboxyl groups of the same protein molecule, the zinc salt must be formed by the replacement from carboxyl groups from two molecules of protein, and be of the type $Zn(Alb)_2$. This would be a larger aggregate than the original protein molecules. If the zinc salt could be adsorbed, as well as enter into chemical reaction in the way described, it is conceivable the adsorbed molecules would surround the protein molecules and inhibit the chemical reaction in which two molecules of protein and one of zinc salt take part. The phenomenon of the inhibition of the formation of zinc protein derivatives by excess of zinc sulphate is, if the explanation suggested above is correct, analogous to the inhibition of formation of complex methyleneimino-peptones, with the difference that the adsorbed salt, in addition to its inhibitory action, can also take part in the chemical reaction by means of which the formation of larger aggregates is brought about. Other similar irregular groups ("unregelmässige Reichen") of colloidal reactions have been described by Neisser and Friedmann ('Münchener Med. Wochenschr.,' 1903, No. 11) and Bechhold ('Zeitsch. Physikal. Chem.,' 1904, vol. 48, p. 355), and others. (For general discussion of these phenomena see 'Freundlich. Kapillarchemie,' Leipzig, 1909, p. 462.)

* 'Journal of Physiology,' 1905, vol. 33, p. 251.

† 'Zeitsch. Physiol. Chem.,' 1901, vol. 33, p. 240.



i.e. neutralisation can take place between the acid group of one globulin molecule and the basic group of another. If either the acid or basic functions, or both, be sufficiently well marked, the product formed by the combination of two molecules will be stable, and will undergo but little hydrolysis in the presence of water (*i.e.* the reaction in the above equation will proceed nearly to completion in the direction indicated by the arrow pointing to the right). The nature of the globulins can be explained by assuming that the undissolved globulin is a complex of this type, which in the presence of water undergoes but little hydrolytic dissociation. That a certain amount of hydrolysis does take place, however, is indicated by Hardy's observation that after repeated washing of serum globulin by water, the washings have always a higher electrical conductivity than the wash water. If salts be added to the water and adsorption on the surface of the dissociated globulin takes place so that it is stereochemically inhibited by the adsorbed salt molecules from forming aggregates by salt formation with other molecules, then the equilibrium between the solid undissociated globulin and water will be disturbed; the more rapidly the salt molecules are adsorbed, the further will reaction proceed in the direction of the arrow pointing to the left in the above equation, and the more the globulin will appear to be dissolved (or to speak perhaps more correctly, to be disaggregated). In offering this explanation as to the nature of the globulins one assumption has been made, viz. that in aggregation under "chemical stimulus" (*i.e.* salt formation) the molecule reaches such large dimensions that it is no longer capable of forming even colloidal solutions, but becomes insoluble. This assumption is supported, however, by certain experimental facts demonstrated by Hardy in the case of serum globulin and by Osborne in the case of edestin.* In their determinations of the solubility of globulins in acids and bases, it was found that the same solvent capacity was possessed by equimolar and not by normal solutions (*i.e.* $HCl = H_2SO_4 = H_3PO_4$; $NaOH = Ba(OH)_2$). This fact can be explained by assuming that in the case of the polybasic acids only the acid salts of the type  are soluble, and the neutral salts of the type  are insoluble; similarly, salts of the type  are also insoluble. In both these

* *Loc. cit.*

latter cases it may be assumed that the molecule has reached such large dimensions that no kind of solution can take place.

The correctness of the conceptions advanced above as to the nature of the formaldehyde-peptone reaction, and of the globulins, receives support in the results obtained in a general study of the action of salts in heterogeneous systems, in which an attempt was made to correlate their action in such systems with the physical properties of their solutions.

The well-known deduction made by Willard Gibbs from thermodynamical considerations, that substances which reduce the surface tensions of solutions tend to accumulate at the surface, which was expressed by the formula

$$-u = \frac{\mathrm{R}}{\mathrm{CT}} \frac{d\sigma}{dc}$$

(where R is the ordinary gas constant, T the absolute temperature, u the excess of molecules accumulating at the surface, c the concentration and σ the surface tension) has been repeatedly applied in late years to the study of adsorption, notably by Donnan, and by Freundlich, and the above formula has at the suggestion of the former been quite recently submitted to experimental verification by Lewis.* From these considerations it might be deduced that the amount of adsorption taking place from salt solutions would be a function of the surface tension of these solutions, the greater adsorption taking place from those solutions possessing a low surface tension. If the suggestions advanced above as to the nature of the formaldehyde-peptone reaction and of the globulins are correct, it should follow that the inhibitory action of salts on the precipitate formation in the former system, and their solvent (or disaggregating) capacity in the latter, are functions of their surface tension.

This hypothesis has been submitted to experimental test, and the results obtained are given in detail below. It was found that in salts of the same series, the lower the surface tension, the greater was the solvent capacity for globulins, and the greater the inhibitory action on the formation of the insoluble methyleneimino-peptone derivative. This general result, however, was found, as already stated, *only when salts of the same series were compared.* The inorganic sodium salts, for example, were found as a general rule to have greater disaggregating capacities than the organic sodium salts having the same surface tension. Sodium salicylate, furthermore, had a far greater disaggregating capacity than sodium benzoate, a salt with very nearly the same surface tension. Sodium formate occupied a position intermediate

* 'Phil. Mag.,' 1908 [6], vol. 15, p. 499, and 1909 [6], vol. 17, p. 466, and 'Zeitsch. physikal. Chem.,' 1910, vol. 73, p. 129.

between the organic and inorganic salts. From these results it appeared as if some property of salt solutions other than their surface tension was concerned in their disaggregating capacity, and the clue as to this property was afforded by certain generalisations on the rate of action in heterogeneous systems, first put forward by Noyes and Whitney,* to explain the rate of solutions of solids in liquids, and subsequently extended to a more general form by Nernst.† These generalisations can be extended to the adsorption phenomena under consideration in the present communication.

If an action takes place in a heterogeneous system, its principal seat will be at the limiting surfaces of the phases. In the case of the solution of a solid substance in water or of a solid base in an acid, the solvent action may be assumed to take place within an infinitely short interval of time. At any particular moment during the course of action, the solid phase will be surrounded by a layer of liquid of different composition to that of the remainder of the liquid phase. To establish equilibrium, molecules will pass through this layer (the diffusion phase), and the rate of action will be a function of the rate at which diffusion will take place. The constant A, representing the reaction rate, may be represented by the equation

$$A = \frac{\text{Area of surface} \times \text{coefficient of diffusion}}{\text{Thickness of the diffusion layer}}.$$

Now the coefficient of diffusion, and probably also the thickness of the diffusion layer, will depend upon another physical constant of the liquid phase, viz., the viscosity—the more viscous this phase, the more slowly the reaction will take place, other conditions being comparable.

These considerations will apply to the globulin system. Excess of globulin in the presence of salt solutions, if the hypothesis as to its nature be correct, forms a triphasic system containing the associated solid globulin aggregates (external phase), the dissociated globulin molecules in colloidal solution (internal phase), and the salt solution (dispersion medium). At the surface of the solid globulin the chief seat of action will be found, and all three phases will co-exist. Equilibrium will depend upon (*a*) the adsorption of the salt molecules by the dissociated globulin, (*b*) the rate of diffusion of these globulin molecules (with or without adsorbed salt molecules) from the solid globulin surface outwards, (*c*) the rate of diffusion of salt molecules inwards towards the same surface to establish equilibrium in the liquid phase, which has been altered in this position by adsorption of the salt from solution. The amount of adsorption is, as already stated, a function

* 'Zeitsch. Physik. Chem..' 1897, vol. 23, p. 689.

† 'Zeitsch. Physiol. Chem.,' 1904, vol. 47, p. 52. See also Brunner, same volume, p. 56.

of the surface tension and concentration.* If, now, the rate of diffusion of the dissociated globulin molecules outwards from the limiting surface, and of the salt molecules inwards towards the same surface, be slow, the concentration of the globulin molecules at this point will be relatively high compared with that of the salt molecules, and a relatively small amount of adsorption will take place. As a consequence the dissociated molecules will tend to reaggregate to form the solid globulin. The reverse will hold if diffusion be rapid. If the conditions be such that a large amount of adsorption takes place, the solid globulin will completely disaggregate and a diphasic system will be formed; on dilution the amount of salt adsorbed will be diminished and reaggregation will take place.

From these considerations it will follow *that the disaggregating action of salt solutions on the globulins is a function of two physical constants of the solutions, viz. the viscosities and the surface tensions. The higher the surface tensions and the viscosities, the smaller the disaggregating capacity.*

Quite similar considerations apply to the inhibitory action of salt solutions on the polymerisation or condensation of the methyleneimino-peptones. Here, again, three phases can co-exist, viz., the poly-product,† the simple methyleneimino-compound in colloidal solution, and the salt solution. If adsorption be sufficiently complete, the poly-product will not be formed, and the system will be diphasic. There is, however, a distinction between the system and the globulin system, which is probably more apparent than real. The precipitate formed by the addition of formaldehyde to Witte's peptone becomes, after a very short interval, insoluble, *i.e.* it will not dissolve in those salt solutions which inhibit its formation; it is, however, soluble in such solutions immediately after it is formed. Possibly a further chemical action, such as dehydration or scission of formaldehyde, takes place after polymerisation, with the formation of a product which can no longer be depolymerised or re-converted into the simple methyleneimino-product by water. The formation of such a product will tend to alter the equilibrium. It may be recalled that serum globulin also becomes insoluble in salt solutions after standing under water for some time, and possibly also undergoes a secondary chemical change of similar nature.

These conclusions have been confirmed by the quantitative investigation of the action of a series of salts on both the systems discussed above. The inorganic sodium salts—chloride, bromide and nitrate, iodide and sulphocyanide, mentioned in the order of decreasing surface tension—have a gradually increasing capacity for disaggregating globulins. Similar results

* See adsorption equation given above.

† This term is used to indicate the more complex product.

were obtained with the sodium organic salts—lactate, acetate, monochloracetate, dichloracetate, trichloracetate, benzoate. It was found, however, that sodium iodide had a much greater disaggregating capacity than, for example, sodium monochloracetate, from which it differed very slightly in the surface tension as measured against air. The inorganic salt solutions, however, are considerably less viscous than those of the organic salts, and hence their disaggregating capacities are greater than those of the latter with the same surface tension. Sodium formate occupies an intermediate position. Its surface tension is somewhat less than that of sodium chloride, and its viscosity is appreciably greater; the latter constant is, however, smaller than those of the other organic salts. Sodium benzoate solution has nearly the same surface tension as that of the salicylate; it disaggregates less, owing to its considerably higher viscosity.

In addition to the passive action in altering the physical properties of solutions, salts may also exert a disaggregating capacity in a more active manner. Hardy* and Mellanby† have shown that the salts of dyad metals (alkaline earths) have a greater solvent action on serum globulin than those of the monad metals; furthermore, salts of dibasic acids dissolve this substance more readily than those of monobasic acids. This action is probably due to the direct attraction of the salt molecules by the proteins, owing possibly to the difference of electric charge. These results have been corroborated. A similar action in the case of edestin is less marked.‡ The salts of the dibasic organic acids have a comparatively small solvent action on edestin; it is, however, greater than that of the salts of monobasic acids with solutions of high surface tension and viscosities. Analogies to these actions have been discovered in the investigation of salt action in other systems about to be described.

If the conceptions advanced above are correct they should apply also to systems other than those containing proteins. The experimental results which confirm them are given in a third communication.

The first of the simpler systems investigated was that containing phenol in the presence of salt solutions. As Rothmund has shown,§ if a mixture of the diphasic system phenol and water be heated, the phenol phase gradually takes up more water, and the aqueous phase takes up more phenol, until a point is reached at which the two phases assume the same chemical com-

* 'Journ. Physiol.,' 1905, vol. 33, p. 251.

† 'Journ. Physiol.,' 1905, vol. 33, p. 338.

‡ See Osborne and Harris, 'Amer. Journal of Physiology,' 1905, vol. 14, p. 151.

§ 'Zeitsch. Physikal. Chem.,' 1898, vol. 26, p. 433.

position, and the system becomes monophasic. This point is known as the "critical solution temperature."

As it has been suggested that solutions of proteins and other hydrophil colloids are diphasic systems analogous to that of phenol and water, in which the amount of water in one of the phases can vary within wide limits, the investigation of the action of salts on this system was of some interest.

It was found that the addition of salts which lower the surface tension decreased the critical temperature of phenol and water. The critical solution temperatures, it is true, do not follow the surface tensions with strict accuracy; it must be remembered, however, that these constants have been measured at ordinary atmospheric temperatures only, whereas the critical solution points are relatively high. Nevertheless, the concordance is sufficiently striking. The viscosity in this case plays but little part, as there is passage of molecules to and fro from both systems. Furthermore, at higher temperatures, the difference of viscosity in different solutions tends to rapidly diminish.

The last series of systems investigated were those of crystalline substances in the presence of salt solutions. The action of salts in these cases was found to be analogous in nearly every respect to their action in systems containing proteins. The salt solutions with low surface tensions possessed a greater disaggregating capacity than those of the same series with higher surface tensions. The viscosity of the solutions also played the same part. In these systems, also, reaction must be considered as taking place at the surface of the two phases. Equilibrium will be attained when disaggregation takes place at the same rate as reaggregation. The lower the surface tension of the solution, the greater the tendency to disaggregate, and the less the tendency to reaggregate; the equilibrium point will be attained with a higher concentration of substance in salt solutions of low surface tension than in those of high surface tension. The more viscous the solution, the sooner will this equilibrium point be attained at the surface of the two phases (*i.e.* the smaller the quantity of solid substance which will have been dissolved), owing to the difficulty of the dissolved substances in diffusing from the solid phase.

These results were arrived at by determining the solubility of the five following substances in the same salt solutions as were employed in the investigations on protein systems—leucine, phenylalanine, caffeine, para-toluidine, and benzamide. The solution capacities of the inorganic salts and organic salts followed in the same order as their disaggregating action on the globulins. Salt solutions with low surface tension, such as sodium benzoate and sodium salicylate, dissolved appreciably more than those of high surface

tensions. In the latter, the solubility of crystalline substances was generally less than that of water; in the former it was generally greater. These results are especially marked in the case of caffeine.

The solution capacities of the salts do not all follow in absolutely the same order in the case of all salts. The rate of diffusion and the surface tension at the junction of the phases could not be directly measured, and in some instances the former exerted a greater effect than the latter. Hence, in some cases, sodium formate has a greater solution capacity than sodium chloride, in others less. If, however, the salts be arranged in series, viz., the inorganic salts, with solutions of low viscosity, the organic salts, with solutions of high viscosity, with sodium formate forming an intermediate class by itself, it will be invariably found that the dissolving capacity of salt solutions of the same series bears a direct relationship to the surface tension.

It was also thought possible that the state of hydration of the salts in solution might exert some influence, in that, owing to combination of salt with water, less water in a normal solution would be available to act as solvent. W. Bilz* and H. C. Jones† have suggested that the abnormally great depression of freezing point of water produced by solutions of salts was due to the formation of hydrates in solution. The molecular depression of the freezing point of various salts was therefore investigated, and it was found that that of the organic salts was, as a rule, greater than that of the inorganic salts. Sodium formate, however, depressed the freezing point of water to about the same extent as did sodium chloride.

If the state of hydration played the chief *rôle* in determining the solubility of a crystalline substance in a salt solution, sodium formate solution should have had about the same solution capacity as sodium bromide and sodium nitrate. The solution capacity was invariably less, and less also in some cases than that of sodium chloride solution, which has a higher surface tension. It does not appear, therefore, as if the state of hydration plays a very direct part in determining the solution capacity of a salt solution, although it may play an indirect part, in that a highly hydrated salt may form a more viscous solution than one less hydrated in solution (compare in tables, viscosities and freezing points of sodium chloride and sodium iodide, sodium chloride and lithium chloride, sodium benzoate and sodium salicylate).

In the case of leucine and phenylalanine, both of which contain a carboxyl group, solutions of the salts of polyvalent metals possessed a greater solution capacity than those of the monovalent metals, the chlorides of the triad metal cerium dissolving more of these substances than any other

* 'Zeitsch. Physikal. Chem.,' 1902, vol. 40, p. 485.

† 'Publications of the Carnegie Institute,' 1907.

solution investigated. This solution capacity was much less marked in the cases of caffeine (which acts only as a base in the presence of strong acids) and benzamide, and was entirely wanting in the case of the base para-toluidine. The solutions of salts of polybasic acids possessed, in the case of leucine and phenylalanine, a slightly higher dissolving capacity than did the salts of monobasic acids of corresponding surface tension and viscosity, and in this respect their behaviour was similar to that in the edestin system. Further investigation on this point is necessary, and also on the electrical charge carried by solid crystals.

Minor differences in the solution capacity of salts of various metals were also noticed which could not be correlated with any physical property. Thus, for example, lithium salts possessed a slightly greater solvent capacity than did those of sodium and potassium (especially in the case of caffeine). Furthermore, strontium salts were intermediate in their action between those of calcium and barium, the calcium salts possessing a greater solvent capacity. These differences were often, however, only faintly marked.

Summary and Conclusions.

I. Complex substances which form colloidal solutions have the capacity of adsorbing other substances from those solutions, which, accumulating on their surface, interfere sterically with their chemical reactions. For this reason such colloidal substances do not in their reactions obey the ordinary laws of chemical mass action.

II. This conclusion has been illustrated by a study of the action of formaldehyde on Witte's peptone. Pauli's observations of the formation of protein salts of heavy metals can perhaps be explained in a similar way.

III. The analogy between the action of salt solutions in inhibiting chemical reaction of the complex proteins, and of their capacity to dissolve globulins, was noticed; the greater the inhibitory action, the greater the solvent power.

IV. These facts suggested an explanation of the chemical character of the globulins. These proteins are here regarded as substances of both markedly acid and markedly basic character, and capable of forming insoluble aggregates by the combination of the acid group of one molecule with the basic group of another; such aggregates will undergo a slight but definite hydrolysis in the presence of water, to form simpler dissociated globulin molecules. In the presence of salts, adsorption will take place on the surface of these simpler molecules, and thus prevent re-aggregation to the solid form and alter the hydrolysis equilibrium. The greater the adsorption of a salt, the greater, therefore, the solvent or disaggregating capacity of its solution for globulins.

V. The adsorption capacity of salts can be correlated with certain physical properties of their solutions. The higher the surface tension and the greater the viscosity, the smaller the adsorption and the disaggregating capacity. These conclusions have been verified experimentally; the influence of these physical properties on the action of salts can, however, be deduced from theoretical considerations, the influence of surface tension from the general study of adsorption phenomena, and that of viscosity by an extension of Nernst's generalisations on the rate of action in heterogeneous systems.

VI. The action of salts on systems other than those containing protein colloids is similar. Investigations have been made of the action of salts on the critical solution temperature of phenol and water, and on the solubility of the following crystalline substances:—*d.l.* leucine, *d.l.* phenylalanine, caffeine, benzamide, and *p.* toluidine.

VII. The critical solution temperature of phenol and salt solutions is a function of the surface tension of the latter.

VIII. The solubility of crystalline substances in salt solutions depends on the surface tensions and viscosities of the latter. In these systems the chief seat of action is at the limiting surfaces of the phases. Equilibrium may be regarded as established at the surfaces when dis-aggregation and re-aggregation are equal. The concentration at which this condition will exist is a function of the surface tension. The viscosity of the salt solution will affect the rate at which diffusion from the limiting surface takes place, and consequently the point at which equilibrium conditions are attained.

IX. The observations of previous observers as to the greater solubility of serum globulin in salts of the polyvalent metals, as compared with those of the univalent metals is confirmed. Similar phenomena were noticed in the case of leucine and phenylalanine. These phenomena were less marked in the case of edestin, and of caffeine and benzamide, and were entirely absent in the case of *p.* toluidine. It is suggested that they are due to the direct attraction of the salt molecules to the surfaces of the solid or disperse phases, possibly owing to the different electrical charges. This would alter the relative tensions of solutions at these surfaces as compared with the measurements of their surface tension against air. The serum globulin is also more soluble in salts of polybasic acids than in salts of monobasic acids. In the case of edestin and of the amino acids, these substances are perhaps very slightly more soluble in salts of dibasic acids than in those of monobasic acid of similar physical properties.* In other cases these phenomena were absent.

X. No evidence of the direct influence of the state of hydration of

* An exact correlation of the solubility capacity with more than one physical constant is not possible with the data available.

the salt in solution on the disaggregating capacity of the latter could be obtained.

The above generalisations as to the action of salts are probably capable of application to other systems. Considerable controversy has arisen as to the nature of the reaction between toxin and antitoxin. Arrhenius and his followers maintain, on the one hand, that it is analogous to the reaction between weak acid and weak base; other investigators hold, on the other hand, that it is of the nature of an adsorption phenomenon. If either or both of the reacting substances are of colloidal nature, adsorption of substances from the reaction medium (serum, etc.) would take place, and even if the reaction be of chemical nature, deviation from the ordinary laws of chemical mass action should be observed, owing to the sterical inhibition by adsorbed molecules. The amount of action would depend upon the medium in which it takes place. Investigations have been already commenced with the object of determining the influence of salts on the toxin-antitoxin reaction, and on other physiological and pathological phenomena.

B. Experimental.—I. The Physical Properties of Salt Solutions.

Throughout this work normal and not molar solutions have been employed. The sodium salts have been generally prepared by adding to 2N sodium hydroxide approximately the amount of acid necessary for neutralisation, one drop of a 1-per-cent. phenolphthalein being used as indicator. Neutralisation was completed by the addition of further quantities of acid in very weak solution, until the pink colour of the phenolphthalein just disappeared. The solutions after cooling were diluted till the normal concentration was attained.

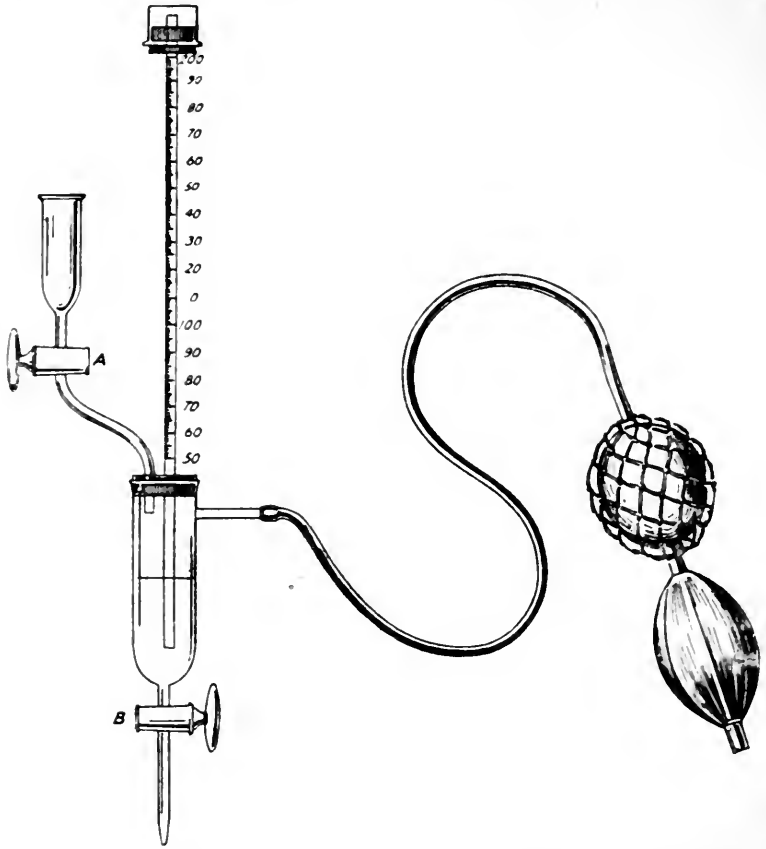
The solutions of chlorides of metals other than sodium were standardised by silver nitrate, volumetrically in the cases of magnesium and the alkali metals, gravimetrically in the case of the other alkaline earths. The sulphocyanide solution was standardised volumetrically by silver nitrate with the use of iron alum as indicator.

The sodium iodide solution was made up by neutralising 2N sodium hydroxide with hydriodic acid, which had been freshly distilled over red phosphorus, and was of only very faint yellow colour. The standard solution was kept in the dark.

Viscosity Determinations.

In order to work with small quantities of solution, a modification of Röntgen and Schneider's apparatus was employed, which is figured in the accompanying sketch.

A fine-bore capillary tube with opal-glass back graduated in the upper part from 50 to 200 mm., the lower mark of which is 50 mm. above an etched zero mark, is inserted through a rubber cork with the lower end downwards into a tube of 24 mm. diameter and 20 c.c. capacity, provided with a side-tube at the upper part near the cork, which is connected with an indiarubber ball, and drawn out at the lower end with a fine, almost capillary, tube, provided with a stop-cock B. Through the rubber cork is



inserted a small funnel provided with a stop-cock A. The vessel into which the capillary tube is inserted has an etched mark on the outside; and, by means of a cathetometer, the capillary tube is so adjusted in the cork that its zero point is exactly opposite this etched mark. The liquid under examination is introduced through A, and by pressure of the rubber ball, and closure of the tap A, is caused to rise in the capillary. Stopcock A is then opened. Liquid is let out from the apparatus by stopcock B, or in by stopcock A, until the lower level is exactly at the zero point, which can be

easily recognised owing to the etched mark. When the liquid has come to rest, the height of the liquid in the capillary tube is read. The levels can be altered by squeezing the indiarubber ball, or by letting liquid out by tap B. The liquid should be passed through the apparatus and up the capillary tube several times until a constant reading is obtained. This is especially important in the case of liquids of high surface tension, which do not readily wet the glass. After using, the apparatus is washed out with water, and then with the fresh liquid of which the physical constant is to be measured. The little cup at the top of the capillary tube is for the purpose of collecting the wash-water and preventing it from soiling the outside.

Between every two or three determinations, a control measurement with pure water was interpolated, so as to ensure that there was no derangement of the zero point, and no error due to alteration of temperature.

All the solutions employed were made up with water which had been distilled in glass vessels over permanganate, and the apparatus and all the vessels employed had been previously soaked in concentrated sulphuric acid, and subsequently washed with the special distilled water before use.

The readings were made with a magnifying glass.

The surface tension determinations given in the accompanying table were the mean of several closely concordant readings (in most cases to within 0·1 mm.), many of them made after long intervals of time.

As unity was taken water, to 100 c.c. of which one drop of 0·5-per-cent. phenolphthalein in 50 per cent. alcohol had been added.* This addition made only a very minute difference in the reading. The specific gravities of the solutions were determined gravimetrically in the ordinary way.

Table I.—Surface Tensions of Normal Salt Solutions (Room Temperature).

Inorganic salts.		Organic salts.	
Sodium chloride	1·032	Sodium formate	1·020
„ bromide	1·024	„ lactate	1·013
„ nitrate	1·023	„ acetate	1·004
„ iodide	1·005	„ monochloracetate	1·002
„ sulphocyanide	1·000	„ dichloracetate	0·970
		„ trichloracetate	0·905
Lithium chloride	1·029	„ salicylate	0·902
Potassium „	1·028	„ benzoate	0·897
Magnesium „	1·030	„ malonate	1·0185
Calcium „	1·028	„ succinate	1·016
Strontium „	1·029	„ tartrate	1·011
Barium „	1·029	„ citrate	1·0105

* See p. 108 for method of preparing standard solutions.

Viscosities of Salt Solutions.

The following measurements were made, as a direct comparison of the viscosities of the salts employed in the investigations was required under varying conditions of temperature, etc. The measurements were made at different temperatures also to determine whether any evidence as to the state of hydration of the salts in solution could be obtained. It was thought that the temperature coefficient would be large in the cases of heavily hydrated salts. The results indicate, however, that the state of hydration has probably only a minor influence on the viscosity. The low viscosity of sodium salicylate solution, compared with that of the benzoate, may possibly be due to the higher hydration of the latter (compare freezing-point determinations below). The results also indicate that sodium iodide and lithium chloride at lower temperatures may be more heavily hydrated than the other halides.

The determinations were made by means of Scarpa's apparatus,* in which, under a pressure somewhat higher than atmospheric, and indicated by means of a water manometer (in the results below, a plus pressure of 200 mm. of water was employed), a definite volume of liquid is made to pass both upwards and downwards through a capillary tube. In the results given below, the time required for passage in both directions is given. If attempts be made to transpose the numbers given below into absolute units by the equation $\eta = \kappa t$, where η = viscosity in absolute units, κ = apparatus-constant, and t = time of passage through capillary, it was found, using Thorpe and Rodger's values for water at different temperatures, that κ gradually became smaller with increasing temperature of the determination. This was due to the error arising from the formation of eddy currents, which were distinctly visible in the determinations made with liquids of low viscosity. As the error due to this factor is greater the lower the viscosity of the liquid, the differences between the determinations should be somewhat larger than those indicated in the table. The error does not detract, therefore, from the comparative value of the results.

The most salient features of the following table are the high viscosities of the organic monobasic sodium salts as compared with the inorganic salts. Sodium formate occupies an intermediate position with a viscosity lower than the highest inorganic salt viscosity (sodium iodide, which only has such a relatively high viscosity at quite a low temperature) but lower than that of any of the other organic salts. The high viscosity of the benzoate compared with that of the salicylate is also to be noted. No other features of the table call for special comment.

* 'Archivio di Fisiologia,' 1905, vol. 2, p. 246.

Table II.—Relative Viscosities of various Salt Solutions (indicated by time (in seconds) of passage of a given quantity of fluid up and down a capillary tube).

Inorganic Salts.

Water.		Sodium chloride.		Sodium nitrate.		Sodium bromide.		Sodium iodide.		Sodium sulphocyanide.	
Temp.	Time.	Temp.	Time.	Temp.	Time.	Temp.	Time.	Temp.	Time.	Temp.	Time.
5·2	89·3	4·7	96·5	5·4	93·0	5·3	94·8	5·4	99·0	4·9	94·1
11·2	77·1	10·3	85·9	10·2	83·9	11·4	84·3	13·0	77·9	12·1	80·0
18·7	64·3	21·1	67·7	20·8	65·9	20·0	70·0	20·2	66·9	21·4	65·8
28·2	52·6	30·9	56·3	29·9	56·1	29·2	59·2	30·0	57·7	30·1	56·4
39·2	44·6	38·8	50·4	39·5	48·5	40·1	49·8	39·5	49·3	39·1	48·6
50·4	39·1	47·5	44·3	50·5	42·3	47·7	44·9	48·1	44·4	51·2	41·9
58·6	36·0	58·8	39·8	57·7	39·4	58·8	40·4	58·7	40·0	58·8	38·8

Lithium chloride.		Potassium chloride.		Magnesium chloride.		Calcium chloride.		Strontium chloride.		Barium chloride.	
Temp.	Time.	Temp.	Time.	Temp.	Time.	Temp.	Time.	Temp.	Time.	Temp.	Time.
5·6	101·3	4·7	85·6	3·4	113·7	4·0	105·4	4·7	102·8	4·3	101·2
11·7	85·4	12·0	74·0	10·9	92·7	11·0	88·2	11·9	88·8	11·7	85·2
21·0	69·8	19·9	64·5	20·0	74·2	20·1	71·0	20·7	71·7	20·5	70·1
30·4	58·1	30·0	52·4	30·6	60·5	28·8	60·3	38·9	52·7	31·8	57·0
40·2	49·8	39·4	46·1	40·2	51·7	39·4	56·9	57·5	43·3	40·0	50·7
49·5	44·1	48·4	40·9	50·0	45·5	51·3	43·3			48·5	45·2
58·9	40·1	58·8	37·2	59·8	40·9	59·4	39·7			58·0	40·7

Organic Salts.

Sodium formate.		Sodium lactate.		Sodium acetate.		Sodium mono-chloracetate.		Sodium di-chloracetate.		Sodium tri-chloracetate.	
Temp.	Time.	Temp.	Time.	Temp.	Time.	Temp.	Time.	Temp.	Time.	Temp.	Time.
3·8	109·8	5·6	138·5	5·0	127·8	4·7	130·7	4·5	141·7	5·4	150·5
11·0	92·0	12·2	114·6	12·1	105·5	12·0	107·4	11·1	116·6	11·7	121·4
20·1	74·4	22·0	88·2	21·2	84·2	21·3	84·1	21·4	88·3	21·2	93·0
29·2	62·2	30·3	73·8	30·8	68·6	30·5	68·9	30·0	74·7	30·5	75·4
38·7	53·0	38·9	61·1	39·3	57·9	39·2	58·1	39·4	61·3	39·0	63·3
50·2	45·5	48·7	52·4	48·8	50·2	48·7	50·7	49·1	52·8	47·4	54·2
58·1	41·4	58·5	46·5	58·6	43·7	59·5	44·0	58·0	46·7	56·2	48·3

Table II—*continued.*

Sodium salicylate.		Sodium benzoate.		Sodium malonate.		Sodium succinate.		Sodium tartrate.		Sodium citrate.	
Temp.	Time.	Temp.	Time.	Temp.	Time.	Temp.	Time.	Temp.	Time.	Temp.	Time.
5·1	141·3	5·3	160·5	4·1	122·2	5·0	124·8	41·1	123·5	5·7	121·9
12·0	117·7	10·5	137·3	10·5	101·2	10·2	107·8	11·8	102·1	10·7	107·4
20·4	93·9	19·8	105·1	20·0	79·8	21·0	82·1	20·9	81·4	21·6	81·7
30·2	74·9	30·3	80·5	30·6	64·0	29·8	68·1	29·5	68·3	29·4	69·9
39·2	62·3	39·1	68·2	40·2	54·0	39·8	57·7	40·0	56·8	39·1	57·4
48·9	53·1	50·2	56·1	49·7	47·8	51·2	47·5	51·0	47·6	48·4	49·5
57·2	48·3	56·8	50·9	60·1	41·7	59·0	44·2	59·0	43·7	58·2	43·9

Molecular Depressions of Freezing Point.

These were determined by the ordinary Beckmann apparatus. The freezing point of normal solutions was directly determined.

Table III.—Molecular Depression of Freezing Points.

Salt.	Δ/M.	Salt.	Δ/M.
Sodium chloride	3·533	Sodium monochloracetate	4·008
„ bromide	3·725	„ dichloracetate	4·311
„ nitrate	3·212	„ trichloracetate	4·510
„ iodide	3·895	„ benzoate	4·095
„ formate	3·677	„ salicylate	3·375
„ lactate	3·940	Lithium chloride	3·851
„ acetate	4·000	Potassium „	3·225

No conclusions as to the *direct* influence of the state of hydration on disaggregating capacity can be drawn from the above tables. The great difference between the molecular depressions in the freezing point of benzoate and salicylate solutions may be noted. This may indicate differences in the state of hydration in solution, and thus differences in the viscosities; the degree of hydration may, therefore, possibly influence the disaggregating powers in an indirect way.

II. The Solubility of the Globulins.

Serum Globulin.

Previous estimations of the solubility of globulin in salt solutions have been made by Hardy* and Mellanby.† The general results indicate that serum globulin is more soluble in salts of polyvalent metals than in those of

* 'Journ. Physiol.,' vol. 33, *loc. cit.*

† 'Journ. Physiol.,' vol. 33, *loc. cit.*

univalent metals, and in salts of polybasic acids than in those of dibasic acids. The results here appended amplify those of the observers just mentioned, in that they demonstrate the influence of surface tension and viscosity on the solvent property.

The solvent (or disaggregating capacity) was determined by titrating 10 c.c. of a given suspension of the globulin with decinormal solution of the salt until the same solution grade was attained. The titration was carried out in a darkened room in a flat-sided trough, at the back of which was placed a constant source of light (electric lamp), the rays of which passed through a paper containing printed matter, held directly against the side of the trough nearest the light. The solution grade point arbitrarily chosen was that at which the printed matter was just legible through the liquid.

The serum globulin was prepared in the ordinary way from horse serum.

In Series I the globulin was purified by solution in ammonia, and precipitation from this solution by dilute acetic acid.

In Series II the sample was simply washed and the washings centrifuged off.

Table IV.—Amount of Decinormal Solutions necessary to add to Suspensions of Serum Globulin to Produce the same Solution Grade.

——	Series I. Strength of suspension 2·74 per cent.	Series II. Strength of suspension 1·79 per cent.
Sodium chloride	—	38·5
„ bromide	—	24·5
„ nitrate	—	22·8
„ iodide	—	16·0
„ sulphocyanide	—	15·5
„ formate	47·0	44·0
„ lactate	48·0	45·0
„ acetate	41·0	43·5
„ monochloracetate	33·0	34·0
„ dichloracetate	22·9	22·2
„ trichloracetate	17·0	14·7
„ benzoate	15·3	—
„ salicylate	12·3	11·25
„ malonate	—	17·5
„ succinate	—	21·0
„ tartrate	—	22·0
„ citrate	—	11·0

These results have been sufficiently discussed in the introduction.

Edestin.

A large number of determinations of the solubility of edestin in salt solutions have been carried out by Osborne and Harris.* The difference

* 'Amer. Journ. Physiol.,' 1905, vol. 14, p. 151.

between the chloride, bromide, and nitrate and iodide are similar to the actions in the case of serum globulin. The results of Osborne and Harris have been extended by determining the solubility of edestin in a series of organic salts, and the results are indicated in the accompanying Table V.

The edestin was prepared from hemp seed in the same way as that employed by Osborne and Harris, the final recrystallisation from sodium chloride having been carried out, after neutralisation of the solution, by allowing the latter to cool in an atmosphere free from carbon dioxide.

The experiments were carried out at ordinary room temperature in the same way as that described in Osborne and Harris' paper. Suspensions of 1 gramme in 10 c.c. of solution or of 2 c.c. in 20 c.c. solution were shaken for some time. When accurate quantitative determinations were made, the mixture was centrifuged, and the nitrogen determined in the supernatant liquid, which was pipetted off.

It was noticed that certain limits of concentration were reached between which the solubility of the edestin rapidly increased (compare the curves in Osborne and Harris' paper). At these limits the edestin became gelatinous on the addition of the salt solution. For these reasons the great differences of the solution capacities of the different salts could be readily demonstrated without the necessity of carrying out nitrogen estimations; in fact, when the edestin became gelatinous, accurate determinations of solubility were difficult.

Table V.—Solubility of Edestin in Sodium Salts of Organic Acids.

Numbers indicate grammes dissolved in 10 c.c. P. indicates that the Edestin forms a paste on addition of Salt.

Concentration salts.	Normal solution.	3N/10.	N/2.	N/4.	N/10.
Formate	Insol.	Insol.	Insol.	Insol.	Insol.
Lactate	„	„	„	„	„
Acetate	„	„	„	„	„
Monochloracetate	Forms paste	6·53	0·87	„	„
Dichloracetate ...	Very sol. P.	Very sol. P.	Very sol. P.	0·45	„
Trichloracetate ...	„	„	„	5·56	Traces only sol.
Benzoate	„	„	„	5·07	„
Salicylate	„	Very sol.	Very sol.	Very sol.	1·46
	Forms gel on addition of 3 gm. to 20 c.c.				
Malonate	1·86	1·65	Traces only sol.	Insol.	Insol.
Succinate	0·65	0·29	„	„	„
Tartrate	1·94	0·78	„	„	„
Citrate.....	2·48	1·83	„	„	„

It will be noticed that the polybasic acid salts have only slightly greater solvent capacities for edestin than those of the monobasic acids. Furthermore

the influence of the valency of the metals is less marked. Interpolating from the curves of Osborne and Harris, it will be found that a 5-per-cent. solution of edestin can be formed under the conditions of experiment employed when the concentration is 5/6 normal. A similar strength edestin solution in sodium chloride is formed in the concentration of 13/20 normal. Bromide forms a 5-per-cent. solution in 9/20 normal (solubility capacity nearly equivalent to that of dichloracetate), whereas sodium iodide can form a solution of this strength in $\frac{1}{4}$ normal concentration, and has a solvent power equivalent approximately to those of the benzoate and salicylate. The higher solvent capacities of the solutions of inorganic salts are again well marked.

Part II.—*On the Action of Formaldehyde on Witte's Peptone.*

This portion of the communication contains the experimental details concerning the reaction of formaldelyde on Witte's peptone, the theory of which has been already discussed in some detail in the first part. The fraction which yields the precipitate with formaldelyde is that containing the more complex polypeptides, as the two following series of experiments show :—

Series I.—Fifty grammes of Witte's peptone were extracted, first with 600 c.c. of cold 80-per-cent. alcohol, and then with 400 c.c.. The alcoholic extract obtained was evaporated *in vacuo*, and the last traces of alcohol were driven off from the residue by taking it up in water and evaporating the solution thus obtained on a water bath. This formed Fraction I (*i.e.* part soluble in 80-per-cent. alcohol). The part of the peptone insoluble in 80-per-cent. alcohol was then extracted with 60-per-cent. alcohol, and the extract treated in a similar way to the 80-per-cent. alcoholic extract; this formed Fraction II. Fraction III was the part insoluble in 60-per-cent. alcohol. Each of the fractions was then made up to a definite volume in water, and the nitrogen in each was estimated. Portions were then taken from each fraction, and diluted so that solutions containing the same amount of nitrogen were obtained; 100 c.c. of each solution contained 0·2156 gramme nitrogen; 40 c.c. of these solutions were taken and to each was added 20 c.c. of 40-per-cent. formaldelyde. After standing, the precipitate was filtered off and nitrogen was estimated in aliquot parts of the filtrate.

In Fraction I the percentage of nitrogen precipitated was 8·3.
„ II „ „ „ 15·6.
„ III „ „ „ 40·0.

Another fraction with the same nitrogen content was prepared from a solution of peptone which had been dialysed for three or four days against running water. Of this preparation, 23·3 per cent. was precipitable by formaldehyde.

Series II.—Fifty grammes of Witte's peptone were extracted successively with two portions of 500 c.c. hot 70-per-cent. alcohol. The insoluble portion (Fraction III) was then washed with cold 70-per-cent. alcohol, and finally with absolute alcohol, and then dried on a water bath. It weighed, when dry, 13·5 grammes.

From the hot aqueous alcohol a second fraction (Fraction II) separated on cooling; this was washed with 70-per-cent. alcohol, then with absolute alcohol and then dried. Fraction I was the portion soluble in 70-per-cent. alcohol.

These were also dissolved up, and solutions made containing the same amount of nitrogen (0·8848 gramme per 100 c.c.).

To determine the complexity, 10 c.c. of each fraction was treated with 5 c.c. formaldehyde and then titrated with N/10 sodium hydroxide by Sörensen's method. The following were the quantities of alkali necessary to neutralise to phenolphthalein :—

Fraction	I	8·9 c.c.
„	II	7·0 „
„	III	5·2 „

To 10 c.c. of each fraction was added 5 c.c. of formaldehyde.

Fraction I was at first clear, and became turbid after standing.
„ II gave an immediate precipitate.
„ III gave a strong clot almost immediately.

After standing for 16 hours the precipitates were filtered off and the nitrogen was estimated in 10 c.c. of the filtrate.

The following were the percentages of nitrogen precipitated by formaldehyde:—

In Fraction	I	25·3 per cent.
„	II	55·7 „
„	III	68·6 „

These results indicate that the larger part of the formaldehyde precipitate is due to the more complex polypeptides contained in the peptone.

Inhibitory Action of Salts.

If minute quantities of caustic alkali be added to the peptone solution, no precipitate will form on the addition of formaldehyde. The formation takes

place, however, after the addition of acids; this addition must not, however, exceed that necessary to produce a turbidity in the peptone solution (precipitation of nucleo-protein). The precipitation is also inhibited by the sodium salts of weak acids. This is due to the fact that the solution, after the addition of aldehydes, contains acids of the type CH : N·R·COOH, which are sufficiently strong to decompose the sodium salts of weak acids. For this reason, salts of weak acids, such as sodium acetate and sodium propionate, do not fall in the same relative position with regard to their inhibitory action as would be expected from the theory connecting viscosity and surface tension with this function. This fact may serve to explain other minor deviations shown in the accompanying table.

In these experiments, of which the results are here recorded, 5 c.c. of a Witte peptone solution were diluted to 10 c.c. with varying quantities of normal solutions of different salts, so that a series of solutions of $2\frac{1}{2}$ per cent. peptone in concentrations varying from N/10 to N/2 of the different salts was obtained. To each dilution was added 2·5 c.c. of a 35-per-cent. formaldehyde solution. The degree of precipitate formation at varying intervals was then noted.

Table giving Inhibitory Action of Various Salts on the Formation of Poly-methyleneimino-peptone.

0 indicates no precipitate. 3 indicates marked opalescence.
1 „ faint turbidity. 4 „ quite opaque mixture.
2 „ opalescence. 5 „ precipitate formation.

The three numbers under each heading indicate the observations after respectively $2\frac{1}{2}$, $4\frac{1}{2}$, and 20 hours.

Concentrations.	$\frac{5N}{10}$.			$\frac{4N}{10}$.			$\frac{3N}{10}$.			$\frac{2N}{10}$.			$\frac{N}{10}$.		
Sodium chloride	3	3+	5	3	+3	5	4	4	5	5	5	5	5	5	5
„ bromide	0	0	0	0	0	0	−1	−1	+3	4	+4	5	5	5	5
„ nitrate	0	0	0	0	0	0	−1	−1	+3	+3	4	5	5	5	5
„ iodide	0	0	0	0	0	0	0	0	0	+3	4	4	5	5	5
„ sulphocyanide	0	0	0	0	0	1	2	2	3	4	4	5	5	5	5
„ formate	0	0	0	−1	−1	1	3	3	3	5	5	5		—	
„ lactate	+1	+1	+1	2	2	2	4	4	4	5	5			—	
„ acetate	0	0	0	0	0	0	0	0	−1	4	4	+4		—	
„ monochloracetate	0	0	−1	2	2	3	3	+3	5	5	5	5	5	5	5
„ dichloracetate	0	0	0	0	0	1	+2	3	5	5	5	5	5	5	5
„ trichloracetate		—		0	0	0	1	1	1	4	4	5	5	5	5
„ benzoate		—		0	0	0	0	0	0	0	0	0	4	4	4
„ salicylate		—		0	0	0	0	0	0	1	1	1	5	5	5
„ malonate		—			—		0	0	0	0	0	0	0	0	0
„ succinate		—			—			—			—		0	0	0
„ tartrate		—		0	0	0	−1	−1	−1	4	4	4	5	5	5
„ citrate		—			—		0	0	0	0	0	0	0	0	0

The general parallelism between these actions and that of the solvent action on serum globulin is manifest, although there are in case of weaker acids noticeable deviations, for the reasons already described.

The salts of polyvalent metals have also a slightly stronger inhibitory action than those of the univalent metals, and this is indicated in the following tables. The experiments here recorded were carried out by adding 10 c.c. of the normal salt solution to 10 c.c. of 5-per-cent. peptone solution, and then precipitating by 4 c.c. of 40-per-cent. aldehyde solution. After standing for a day the precipitate was filtered off, and the nitrogen was estimated in aliquot parts of the filtrate. The total nitrogen was estimated also in a corresponding portion in which no precipitation took place, and in a portion in which 10 c.c. of peptone was diluted with 10 c.c. of water instead of salt solution.

Table giving the Relative Amount of Precipitation in Presence of Various Chlorides. $2\frac{1}{2}$ per cent. peptone in N/2 solutions of salts.

	Chlorides.		Chlorides.
Water	100·0	Magnesium	25·5
Lithium	49·0	Calcium	4·5
Sodium	49·5	Strontium	24·5
Potassium	40·0	Barium	26·0

Part III.—*On the Solubility of Phenol and certain Crystalline Substances in Salt Solutions.*

The theory and discussion of the results recorded in this part have been already dealt with in some detail in Part I.

Critical Solution Temperature of Phenol and Salt Solutions.

The compositions of the two phases, phenol and water, were investigated in detail many years ago by Rothmund.* It may be recalled that if a mixture of the two substances be heated, the phenol phase becomes richer in water, and the aqueous phase richer in phenol until a point is reached when the system becomes monophasic. The temperature at which this will happen will depend upon the readiness with which disaggregation takes place, and should consequently be a function of the surface tension at the limiting surfaces of

* 'Zeitsch. Physikal. Chem.,' 1898, vol. 26 p. 433.

the phases. The lower the surface tension of the salt solution therefore, the lower should be the critical solution temperature. This hypothesis is fully borne out by the results recorded in the accompanying table.

Fifteen grammes of crystalline phenol were mixed with 25 c.c. of N/10 salt solutions in a wide-mouthed test-tube provided with a stirrer, and with a thermometer inserted into the mixture. This was inserted into a litre beaker containing water, which was also provided with a stirrer, and which was slowly heated on a sand bath; both the mixture in the test-tube and the water were continually stirred the whole time. As critical solution temperature is arbitrarily chosen that point at which the phenol-salt solution mixture is converted from an opaque to an opalescent fluid, a process which takes place within the interval of one-tenth of a degree. On further heating the opalescent fluid gradually becomes clear; on cooling again, with continual stirring, opalescence and final opacity reappear, and the point at which the opalescent fluid becomes opaque is only a fraction of a degree lower than the point observed when the change took place in the reverse direction.

With normal solutions of the salts of lower surface tensions, such as sodium trichloracetate, the system is monophasic even at quite low temperatures (4° C.).

Table I.—Critical Solution Temperatures of Phenol and N/10 Salt Solutions.

Solutions.	Temperature.	Solutions.	Temperature.
Sodium chloride	74·3	Sodium formate	70·0
„ bromide	73·7	„ lactate	68·5
„ nitrate	71·8	„ acetate	66·9
„ iodide	72·1	„ monochloracetate	66·1
„ sulphocyanide	68·2	„ dichloracetate	63·1
		„ trichloracetate	58·0
Lithium chloride	74·3	„ benzoate	49·1
Potassium „	73·2	„ salicylate	49·3
Magnesium „	75·2	„ malonate	77·1
Calcium „	75·0	„ succinate	74·8
Strontium „	74·9	„ tartrate	77·1
Barium „	75·0	„ citrate	77·0
		„ chloride	74·3

Solubility of Crystalline Substances in Salt Solutions.

The benzamide, caffeine, and *p*-toluidine were Kahlbaum's preparations.

The phenylalanine was prepared synthetically by the method of E. Fischer.*

The *d.l.* leucine was prepared directly from commercial isoamyl alcohol. From the latter, isovaleraldehyde was prepared by the method of Bouveault and Rouszet† by dropping the alcohol into a warmed bichromate mixture,

* 'Ber.,' 1904, vol. 37, p. 3062.

† 'Bulletin de la Soc. Chim.,' [3], vol. 11, p. 301.

and allowing the aldehyde to distil off as soon as it is formed. The latter, after separating from the aqueous layer, was dried over fused sodium acetate, and then fractionated with a Young rod and disc still-head and the fraction boiling below 120° was separately collected. This was converted into the bisulphite compound, which was washed with ether, and air-dried, decomposed with a small excess of bicarbonate and the aldehyde then distilled off. To the aldehyde was then added, little by little, and with constant cooling, half the volume of ordinary concentrated ammonia, and the mixture, after standing a day, completely solidified. The valeraldehyde ammonia compound was then washed with ether, and air-dried. The compound from 300 grammes aldehyde was then treated in three portions with 300 c.c. water, and to the suspension was added 150 c.c. anhydrous hydrocyanic acid, diluted to 270 c.c. with water. The cyanammonia compound was then hydrolysed, and the remainder of the preparation completed by the method of E. Fischer.* From 300 grammes of aldehyde were obtained 200 grammes of twice recrystallised pure inactive leucine.

The determinations of solubility were carried out by mixing 1 gramme (or more if 1 gramme were insufficient for complete saturation) of the crystalline substance with 30 c.c. of the salt solution in short wide-mouthed test-tubes, which were then tightly corked, and clamped on to a rotating axis in a thermostat, and thus, by means of a motor, kept in a state of constant motion, generally for a period of 36 hours. At the end of this time the liquid was filtered from the undissolved solid by means of a water pump through a perforated platinum plate covered with asbestos, into a flask with a narrow neck graduated in tenths of a cubic centimetre between 20 and 30 c.c., which was carefully calibrated before use, and which was provided with a side-tube near the mouth of the flask, turned upwards so as to connect with the water-pump for suction. The whole apparatus was immersed in the thermostat during filtration, and the amount of liquid filtered was directly read.

The nitrogen was determined in this liquid by means of Kjeldahl's method, except in the case of the nitrates and sulphocyanides. In both these cases the leucine and phenylalanine were estimated by Sörensen's formaldehyde titration method, and in determinations of the solubility of other substances in sulphocyanide the undissolved crystallised substance left on the filter-plate was dissolved in some organic solvent, and the nitrogen determined in this solution after filtering through blotting-paper. In the latter case there is a slight error, owing to the fact that it is impossible to wash the crystals. The Kjeldahl method of estimation was, in the case of

* 'Ber.,' 1900, vol 33, p. 2370.

phenylalanine and leucine, preferred to the Sörensen method, as the end point of titration is a certain pink colour, and not the first appearance of pink. Nevertheless, a series of solubility determinations carried out by this method in the case of leucine agreed well with the results obtained by the Kjeldahl method.

The ammonia was distilled off through hard-glass well-cooled condensers, to avoid the action of the hot liquid on the glass. Sodium alizarine sulphonate was the indicator used for titration, and the ammonia present in the various reagents as an impurity was estimated and the necessary corrections made. It was only found in the sulphuric acid and lithium chloride, and the correction in each case was only a fraction of a cubic centimetre.

Table II.—Solubility of Leucine and Phenylalanine. Temperature $23°{\cdot}7 \pm 0°{\cdot}1$ C.

	Leucine.			Phenylalanine.		
	A. Mg. mol. per litre.	B. Grammes per litre.	C. Relative solubility, $H_2O = 100$.	A. Mg. mol. per litre.	B. Grammes per litre.	C. Relative solubility. $H_2O = 100$.
Water	73·1	9·57	100·0	85·2	14·06	100·0
Sodium chloride	63·9	8·37	87·4	72·6	11·98	85·2
„ bromide	68·9	9·03	94·3	83·2	13·77	97·7
„ nitrate	68·9	9·03	94·3	86·6	14·29	101·6
„ iodide	72·7	9·52	99·4	93·4	15·41	109·6
„ sulphocyanide	78·2	10·24	106·9	99·9	16·48	117·3
„ formate	65·1	8·53	89·0	75·7	12·49	88·8
„ lactate	53·9	7·06	73·4	58·6	9·67	68·8
„ acetate	57·6	7·55	78·8	66·9	11·04	78·5
„ monochloracetate	61·4	8·04	84·0	74·6	12·31	87·5
„ dichloracetate	62·5	8·19	85·5	80·0	13·20	93·9
„ trichloracetate	66·2	8·67	90·6	86·6	14·29	101·6
„ benzoate	68·3	8·94	93·4	96·1	15·86	112·8
„ salicylate	81·3	10·65	111·2	120·8	19·93	141·7
„ sulphate	59·3	7·77	81·1	69·4	11·45	81·4
„ malonate	60·0	7·86	82·1	70·6	11·65	82·8
„ succinate	57·7	7·56	78·9	69·1	11·40	81·1
„ tartrate	57·2	7·49	78·2	65·2	10·96	76·5
„ citrate	61·2	8·02	83·7	72·6	11·99	85·3
„ chloride	63·9	8·37	87·4	72·6	11·98	85·2
Lithium „	69·2	9·06	94·6	81·4	13·53	95·5
Potassium „	65·4	8·57	89·5	77·5	12·79	90·9
Magnesium „	81·6	10·69	111·6	94·3	15·56	110·6
Calcium „	87·4	11·49	119·5	106·2	17·52	124·6
Strontium „	83·0	10·87	113·5	96·5	15·92	113·3
Barium „	78·8	10·32	107·8	97·8	16·14	114·7
Cerium „	164·6	21·56	225·1	175·0	28·87	205·4

The results are recorded in three columns. In Column A the solubility in milligramme molecules per litre is given; in Column B the solubility in grammes per litre of solvent; and in Column C the relative solubilities, that in water being taken as 100.

Table III.—Solubilities of Caffeine, Benzamide, *p*-toluidine. Temperature 23°·7 ± 0°·1 C.

	Caffeine.			Benzamide.			*p*-toluidine.		
	A.	B.	C.	A.	B.	C.	A.	B.	C.
Water	98·5	19·109	100·0	105·6	12·78	100·0	66·6	7·126	100·0
Sodium chloride	65·7	12·75	66·7	80·5	9·74	76·2	50·3	5·38	75·5
„ bromide	105·3	20·43	106·9	89·9	10·88	85·2	56·0	5·99	84·5
„ iodide	225·6	43·77	229·0	105·2	12·73	99·9	68·4	7·32	102·7
„ sulphocyanide	288·0	55·87	292·4	112·2	13·57	106·2	135·0	14·44	202·7
„ formate	56·7	11·00	57·5	79·7	9·64	75·4	42·7	4·57	64·1
„ lactate	46·9	9·10	47·6	77·5	9·38	73·3	36·8	3·93	55·2
„ acetate	48·9	9·49	49·9	80·0	9·68	75·7	41·4	4·43	62·1
„ monochloracetate	84·9	16·47	86·2	101·9	12·33	96·5	reaction	—	—
„ dichloracetate	167·1	32·34	169·6	109·2	13·21	103·4	66·4	7·10	100·0
„ trichloracetata	416·6	80·82	422·9	137·9	16·69	130·5	71·7	7·67	107·6
„ benzoate	776·3	150·60	787·8	164·9	19·95	156·1	81·7	8·74	122·6
„ salicylate	1188·0	230·47	1206·1	244·7	20·61	231·7	118·9	12·72	178·5
„ sulphate	49·4	9·58	50·1	67·9	8·21	64·3	38·4	4·11	57·7
„ malonate	42·3	8·20	42·9	70·2	8·49	66·4	29·2	3·12	43·8
„ succinate	44·1	8·55	44·7	72·0	8·71	68·1	37·4	4·00	56·1
„ tartrate	44·1	8·55	44·7	68·6	8·30	64·9	34·1	3·65	51·0
„ citrate	41·0	7·95	41·6	69·5	8·41	65·8	31·5	3·37	47·3
„ chloride	65·7	12·75	66·7	80·5	9·74	76·2	50·3	5·38	75·5
Lithium „	110·2	21·80	114·0	89·2	10·69	83·5	56·9	6·08	85·9
Potassium „	68·0	13·19	69·0	83·7	10·13	79·2	52·6	5·63	78·9
Magnesium „	83·6	16·22	84·8	90·1	10·90	85·3	53·1	5·68	79·7
Calcium „	84·6	16·41	85·9	93·4	11·26	88·4	51·5	5·51	77·3
Strontium „	79·2	15·36	80·4	91·0	11·01	86·1	53·2	5·69	79·9
Barium „	76·6	14·86	77·7	89·2	10·79	84·4	47·7	5·10	71·7

In the above table the salts are divided into five subdivisions, viz., the inorganic monobasic salts, or salts of low viscosity, sodium formate, a salt with viscosity between those of the inorganic salts and the other organic salts, the organic monobasic salts with high viscosities, the salts of polybasic acids, and salts of metals other than sodium. The monobasic sodium salts are placed in descending order of their surface tension in the columns.

This arrangement indicates at a glance the generalisations arrived at in the theoretical introduction to the three papers.

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AURICULAR FIBRILLATION AND COMPLETE IRREGULARITY OF THE VENTRICLE.

By THOMAS LEWIS (of University College Hospital Medical School).*

AMONGST the many forms of irregularity of the heart which are met with in clinical study, there is one which stands out pre-eminently; it is the commonest of all the varieties of disturbance of the normal or regular and sequential contraction of the several cardiac chambers. So frequent is it, that of instances of persistent heart irregularity it constitutes approximately 50 per cent. A general hospital always exhibits one or more cases in its wards, and often-

* The expenses connected with the researches upon which this outline is based have been defrayed by grants from the Royal Society and the British Medical Association.

the influence of acceleration of the auricular rate upon impaired conduction; of ascertaining the effect of premature ventricular contractions, single or successive, upon the same transmission from auricle to ventricle; of studying

times several examples of it are to be found side by side in the same ward.

It occurs in especial association with two types of clinical case; its presence is almost the rule in the later stages of mitral disease, more particularly mitral stenosis; it is found in the absence of valvular disease in the widespread and general degeneration of the cardio-vascular system of more elderly subjects.

The irregularity is of a special and specific nature; it is absolute; for the length of the pause between adjacent beats shows no constancy, and, as opposed to the circumstances in other types of arrhythmia, no relationship can be discovered between the lengths of the pauses in any two sections of the curves obtained. The remaining arterial feature identified with the condition is the absence of definite proportion between the strength of a pulse beat and the pause which precedes it.

My object is to show that this irregularity of the ventricle has its origin in inco-ordinate contraction or fibrillation of the auricle.

The irregularity in question is invariably accompanied by a type of venous curve known as the "ventricular form of venous pulse," a fact which may be adduced as evidence that we are dealing with a special and single type of arrhythmia. (Diagrams illustrating the auricular and ventricular forms of venous pulse, and the differences between them, were shown.) The most noteworthy feature of the venous curves is the absence of any sign of the normal auricular contraction, and this peculiarity is in accordance with the evidence derived from other sources, *i.e.* œsophageal curves, cardiograms, and electro-cardiograms. Yet, while such records show in the clearest manner that in complete irregularity of the heart the normal auricular activity is in abeyance, autopsies obtained in such cases not infrequently furnish the information that the auricle (speaking of right and left auricles as a whole) is hypertrophied. Moreover, while the cases are under observation during life, it is by no means uncommon for the irregularity to vanish abruptly and give place to a regular and normal action of the heart. This signal return to the normal mechanism is accompanied by a reappearance of all those signs of normal auricular contraction which are customarily obtained in the normal condition. Therefore, while in the stage of complete heart irregularity we are justified in denying the presence of normal auricular activity, it cannot be legitimately held that in the same stage the auricle is inactive. The inactivity

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or paralysis of an area of cardiac muscle, capable of contraction and under conditions suitable for contraction, for an appreciable space in time, is a phenomenon not only unknown in experiment, but probably non-existent. Consequently we have to assume that in complete heart irregularity the auricle is active.

(Lantern slides and diagrams were shown to illustrate the normal electro-cardiogram, and the change which takes place in it at the onset of the arrhythmia under consideration.)

The type of electro-cardiographic curve obtained in complete heart irregularity differs from the normal in a notable respect. The normal auricular variations are replaced by a series of irregular oscillations occurring at rates lying approximately between 400 and 800 per minute. The oscillations are invariably present if sufficiently sought, and are unique. Their point of origin may be demonstrated by leading off to the galvanometer from various parts of the body. They are not derived from the somatic musculature, for they are maximal, not when a large area of voluntary muscle lies between and beneath the electrodes, but when the heart is similarly situate. Furthermore, the oscillations are most prominent when, of the various leads from the front of the chest, that lead is chosen in which the right or superficial auricle is most closely approached. (Slides and diagrams illustrating the leads and resultant curves were shown.) We have direct and convincing evidence of the origin of the oscillations in the heart and in the neighbourhood of the auricle. By leading from various areas of the chest wall, it is possible to obtain curves which are almost purely auricular and ventricular respectively; the usual arm and leg leads give curves which are composite and frequently obscure, for the auricular and ventricular variations are superimposed in them. By adopting leads which yield a more exact analysis, the auricular curve is shown to be highly abnormal, and the ventricular curve, considering the curve yielded by the individual beat, is seen to be of the normal type, consisting as it does of the usual variations; the ventricular curve presents none of those oscillations which are under consideration.

The conclusion warranted is that the auricle is active, and that its activity is of a special nature.

Now auricular activity is of two forms; either it is co-ordinate or it is inco-ordinate. Of the former, or co-ordinate auricular activity, there is no trace in any of the curves obtained. We are left, as a

consequence, with the assumption that in complete irregularity of the heart the action of the auricle is inco-ordinate.

Inco-ordinate contraction of the auricle is well known to experimentalists, and passes under the names "auricular fibrillation," or "auricular delirium." In the presence of this mechanism, the auricle is in permanent diastole and, in place of the quick, regular, and universal contraction of its musculature, a flickering or tremulous movement is seen upon its surface. The fibres of which the upper chamber is composed appear to contract independently, and in an entirely disorderly fashion.

The evidence in regard to complete irregularity of the heart, so far as it has been taken, seems to point to some such mechanism in the auricle, and it remains to institute a comparison, direct and searching, between two conditions, namely, complete irregularity as observed clinically, and auricular fibrillation as it is known experimentally.

The Comparison.

(Lantern slides illustrating the several points were shown.)

The Arterial Pulse.—It has been said that in complete irregularity of the heart the pulse presents certain distinctive features. The absolute irregularity and the absent relationship between force of beat and length of preceding cause are the most prominent. In addition the increase of rate as compared to the normal may be noted. Auricular fibrillation in animal experiment yields precisely similar phenomena.

The Venous Pulse.—(*a*) The ventricular form of venous pulse is one of the fundamental signs present in the clinical condition. It may take upon itself several forms. Thus, it may be constituted by a series of high, square-topped plateaux, or by groups of two or more waves, the waves separated by deep depressions. The ventricular form of venous pulse is always found in experimental auricular fibrillation, and its several clinical varieties are duplicated. In both clinical and experimental instances the same constant feature is discovered: prominent and rapid upstrokes are absent during the diastolic reaches of the curve. The conspicuous waves are strictly confined to systole.

(*b*) In certain instances small oscillations are present upon the clinical venous curves; they are very rapid in their succession, and are seen to advantage in diastole when the heart beat is slow. Precisely similar waves are met with in venous curves taken from

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the dog, when the auricle is fibrillating and the ventricle is beating slowly as a result of vagal stimulation.

The Electro-Cardiographic Curves.—The curves in complete irregularity of the heart and those obtained by similar methods from animals in which auricular fibrillation has been induced are identical in every respect.

1. The peak R, the first sign of ventricular contraction, occurs in each condition, and is the only clean cut variation in either case. It is an indication of the supraventricular origin of the ventricular contraction in both instances.

2. The height of the peaks R is not proportional to the length of the preceding pauses; neither is it proportional to the strength of the corresponding arterial pulsations. These are features common to the two conditions.

3. There is a good deal of evidence to show that the height of the peak R is increased, as compared to the normal, in both conditions.

4. The irregular oscillations which are present in complete heart irregularity and replace the usual auricular variations are likewise found in experimental auricular fibrillation, and are of a similar nature. In the clinical instance they can be traced to the neighbourhood of the auricle. In the experimental instance they can be shown unequivocally, by similar methods and by simultaneous electric and myocardiographic curves, to be auricular in origin, and to be dependent upon fibrillation in that chamber.

Clinically the oscillations vanish when the complete irregularity ceases; similarly they disappear in experiment when the fibrillation ends, spontaneously or otherwise.

The oscillations show the same variations in form and rate from case to case and experiment to experiment; variations which are to be expected in the latter, from our knowledge of the variations in the myocardial movements.

Conclusions.

In brief, the clinical and experimental phenomena appear identical when examined by all means within our reach; the evidence, as a whole, is abundant, and can only lead to the conclusion of an identical mechanism in the two conditions. Auricular fibrillation, be it remembered, is provoked experimentally with the greatest ease; the auricle is ever ready to pass into this inco-ordinate state.

the influence of acceleration of the auricular rate upon impaired conduction; of ascertaining the effect of premature ventricular contractions, single or successive, upon the same transmission from auricle to ventricle; of studying

There is, therefore, less hesitation in regarding it as a common type of disordered mechanism in the human heart. In the dog, when once established, it may persist for several hours, and appears to create but little disturbance in the peripheral circulation. Why, therefore, may it not continue in the human chest, where surrounding conditions are more natural, for days, months, or even years.

Considering the frequency of complete irregularity of the heart in the human subject, we must assume an equal frequency of auricular fibrillation, for all cases of complete irregularity of the heart are, so far as we know, associated with the ventricular form of jugular pulse and the typical electro-cardiographic curves, and the evidence allows of no other conclusion but that in such cases auricular fibrillation is present.

There is no hesitation in concluding that a patient exhibiting (1) complete heart irregularity, (2) the ventricular form of venous pulse, and (3) the characteristic electro-cardiogram, is the subject of auricular fibrillation. We have full warrant for such a conclusion. And as we know that it can only be in very exceptional instances that complete irregularity is present in the absence of one or both of the remaining signs (for such a circumstance has never been recorded), we are justified in the further conclusion that the vast majority of, if not all, cases of complete irregularity of the heart are the outcome of this fibrillation. That is to say that, in 50 per cent., or thereabouts, of all cases of persistent ventricular irregularity in man, the auricle (right and left) is in inco-ordinate contraction or fibrillation.*

* Since this paper was read (December 13th, 1910) my full article containing the complete evidence and extended observations has been published ('Heart,' 1909-10, vol. i, p. 306). At the same time Rothberger and Winterberg's full paper appeared ('Pflüger's Archiv,' 1910, vol. cxxxi, p. 387). I have since been able to establish the fact that a similar irregularity occurs in horses, and in two such instances on examining the hearts, as they were beating *in situ*, have obtained a full confirmation of the proposition put forward, namely, that the irregularity in question is the result of auricular fibrillation.

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THE INFLUENCE OF CERTAIN FACTORS UPON ASPHYXIAL HEART-BLOCK

By THOMAS LEWIS[1] and B. S. OPPENHEIMER

With Plates 23–25

The experimental study of auriculo-ventricular heart-block in the intact animal is not without difficulty, for at the point at which the bundle may be divided with convenience, it lies in the septum separating the ventricles or the septum between the right auricle and left ventricle. To produce a lesion of the bundle, by section and with certainty, necessitates transfixation of this septum. As a consequence a communication between left ventricle and either right auricle or right ventricle is a customary result. The method of incision with the heart beating *in situ* is therefore impracticable as a routine procedure.

The difficulty may be avoided by the employment of sutures, so arranged as to include the bundle, and this method has been adopted by the Berne school. But it is apparent that the placing of such sutures is not accomplished with facility; a single suture is frequently insufficient, and a large number of the experiments are totally abortive. When experiments are directed not merely towards the production of heart-block, but towards the further investigation of heart-block once produced, it becomes essential that more certain means of inducing it should be obtained. This end has been accomplished by Erlanger and his co-workers by means of a special clamp, devised to penetrate the intra-ventricular septum, and to include between its jaws the upper portion of the septum, the bundle and the tissues lying directly at the base of the ascending aorta.

In a paper which appeared in a recent number of *Heart*, one of us, working with Mathison (3), described a series of experiments upon the asphyxial heart, originally observed by Sherrington (5). It was clear that we were in possession of a sure means of producing heart-block in its several grades, and that as a consequence we could conveniently utilize asphyxia as a method of producing heart-block and could study the heart-block so produced.

The present observations were undertaken with the object of determining the influence of acceleration of the auricular rate upon impaired conduction; of ascertaining the effect of premature ventricular contractions, single or successive, upon the same transmission from auricle to ventricle; of studying

[1] Working under the tenure of a Beit Memorial Research Fellowship.

the influence of slight grades of conduction damage upon the retrogression of impulses from ventricle to auricle; and of determining the influence of vagal stimulation upon partial heart-block. Some of the observations have already been undertaken by Erlanger (2) and Erlanger and Hirschfelder (1), who produced heart-block by compression of the bundle with their specially devised clamp. We considered it essential to confirm in asphyxial heart-block the observations made by these writers on heart-block resulting from mechanical compression, and if possible to extend their observations.

Method. Cats have been employed exclusively. They have been anaesthetized with a preliminary injection of urethane, in an approximate dosage of one and a half grams per kilogram of body weight, and by the subsequent administration of a sufficiency of chloroform. In the earlier experiments we employed the intact chloroformed and curarized animal; in the later observations we decapitated the cats. In the earlier experiments we sometimes cut the vagi and sometimes preserved them. We have found no essential difference in our results according to the adoption of one or other of these several procedures.

Premature beats were induced by means of induction shocks, single or successive and regular, and applied to auricle or ventricle. The fish-hook electrodes attached to auricle and ventricle were introduced through small windows in the chest-wall, which were subsequently closed, so that the heart might lie within the thorax in as natural a position as possible. No air was permitted to remain in the pleural spaces.

Asphyxia was provoked by the suspension of artificial respiration. Preliminary observations were made to ascertain the times of the onset of the several grades of heart-block in the individual animals. In this manner the auricle and ventricle could be stimulated at will, during a phase of any degree of heart-block manifested by the animal under investigation.

The heart-block which occurs in asphyxia progresses from a slight to a higher grade, and as a general rule, when a particular grade of heart-block is established, there is no break-back to a lower grade, so long as the asphyxia persists. A special factor, as for example auricular tachycardia, may temporarily increase the degree of such a slowly progressive heart-block. When one is studying the effect of various factors upon the original degree of asphyxial heart-block, a change from a lesser to a greater grade may be pronounced as due to the interfering factor, and not as constituting a step in the regular succession of heart-block changes produced by the asphyxia itself when, at the cessation of the interference, that grade of heart-block is re-established which existed prior to such interference. We take as our criterion of the production of an increased grade of heart-block by an interfering factor, the constant appearance of the increase of grade at a time when the interference occurs; and reject all observations in which the pre-existing degree of heart-block fails to reappear immediately upon, or soon after, the cessation of stimulation. For under the last-mentioned circumstances it would be impossible to declare that the increased grade of heart-block is due to stimulation, and not to the asphyxia *per se*.

Asphyxial heart-block is associated with considerable distension of the auricular portion of the heart, and although heart-block be observed by inspection of the chambers, myocardiograms are difficult to obtain on account of the feeble movement present in the auricle at such times. We have consequently employed the string galvanometer, leading from the right fore-leg and left hind-leg, as the most convenient and certain method of obtaining records.

The Effects of Auricular Tachycardia.

In control observations, in which the transmission interval is of normal length (for cats, 0·08 to 0·12 sec.), auricular tachycardia, resulting from a succession of regular induction shocks thrown in at a more rapid rate than the natural heart rhythm, usually produces little or no effect upon the conduction time. On occasions, however, and with very rapid tachycardia, we have noticed a reduction of the P–R interval.

The effect of an auricular tachycardia upon conduction during the earliest phase of asphyxial heart-block, namely, when the P–R interval is prolonged, varies considerably in different animals; but it is consistent in this respect, that it invariably induces an enhanced degree of block. Thus the acceleration of auricular rate may cause a further and gradual increase of this P–R interval, and the increase may be followed to a point at which single blocked beats occur, or at which 2 : 1 heart-block is established (Figs. 1 and 2). On other occasions, an abrupt rise in the degree of heart-block may be seen. A prolonged P–R interval may give place immediately to a 2 : 1 and eventually to a 3 : 1 rhythm; on rarer occasions, but not uncommonly, complete dissociation supervenes (Fig. 2). As a rule a short strip of curve intervenes between the prolonged P–R interval and the complete heart-block stage, and during such a period a high grade of partial block is present, e. g. 2 : 1 or 3 : 1 heart-block, or a succession of ventricular beats occurring at irregular intervals in response to auricular impulses (Fig. 3). Thus to illustrate the last phenomenon, a prolonged P–R phase may be succeeded at the supervention of auricular tachycardia by a 2 : 1 then 6 : 1, 5 : 1, 4 : 1, 6 : 1, 3 : 1 cycle. Such periods constitute the nearest approach which we have encountered during the present experiments to stoppage of the ventricles as described by Erlanger and Hirschfelder. The longest intervals of 'stoppage' were of about 2 seconds' duration.

When 2 : 1 heart-block has been established as a result of asphyxia, a tachycardia arising in the auricle varies in the effect according to the rate of such tachycardia and according to the duration of the 2 : 1 phase. Thus in the early stages of 2 : 1 asphyxial heart-block an increase of auricular rate may actually lead to an increase of ventricular rate with a maintenance of 2 : 1 rhythm (Fig. 5). This fact does not necessarily signify the absence of an increased obstruction to the passage of auricular impulses at such times. The phenomenon is not observed during the later stages of a 2 : 1 rhythm, for at such times the

2 : 1 phase gives place to higher grades of heart-block. Variation in the results in the earlier and later stages of 2 : 1 heart-block meets with an obvious explanation. During the whole of the asphyxial experiment, the grade of the heart-block is increasing, although the increase is only conspicuous at the beginning and at the termination of the 2 : 1 phase. During the early stages of the 2 : 1 phase the junctional tissues are capable of transmitting impulses at a faster rate than they are actually called upon to do, whereas towards the end of the 2 : 1 stage they are transmitting impulses at the maximal rate.

A 2 : 1 heart-block, when fully established, may be converted by auricular tachycardia into 3 : 1, 4 : 1, or complete heart-block; in the last instance, with or without the interpolation of cycles of partial heart-block of higher grades (Fig. 4). At the cessation of stimulation a partial over-recovery is observed, i. e. a temporary return to a lower grade of heart-block than that which prevailed before the stimulation. For example, we have observed a 2 : 1 block converted by an auricular tachycardia to successive cycles of 6 : 1, 3 : 1, 4 : 1 block; while on cessation of the auricular tachycardia one cycle of 2 : 1 block occurred and was followed by three 1 : 1 cycles, accompanied by a prolonged P–R interval. At a later period there was a return to a persistent 2 : 1 rhythm.

A phenomenon which we have not uncommonly encountered in decapitated cats, and for which we can offer no explanation, may be observed at the termination of auricular tachycardia induced during a stage of asphyxial heart-block. The whole heart may stand still for prolonged periods. There is eventual recovery. The periods of stand-still of the heart have extended through varying intervals up to three seconds. They may occur during the stages of prolonged P–R interval, or 2 : 1 heart-block (Fig. 3).

The Effects of Induced Ventricular Beats upon Auriculo-Ventricular and Ventriculo-Auricular Conduction.

The effect of single excitations, applied to the ventricle, is variable from animal to animal, but is most pronounced where a considerable grade of heart-block is present; for example, a single premature beat, falling just before an expected response of ventricle to auricle during a 2 : 1 heart-block stage, hinders this response and the response to the succeeding auricular impulse. That is to say, the single premature beat replaces the usual ventricular beat, which is a response to one of the alternate auricular impulses. Even though the premature ventricular contraction falls earlier in a 2 : 1 cycle, so that the succeeding auricular impulse falls clear of the refractory period, the same events occur; there is an absence of response, both to this and the succeeding auricular impulse (cp. Erlanger's experiments upon compression heart-block).

A further exaggeration of this phenomenon is shown in Fig. 6. A single premature ventricular beat occurring during a 2 : 1 heart-block phase produces an absence of response to three auricular contractions, and the first ventricular beat is apparently ideo-ventricular in origin.

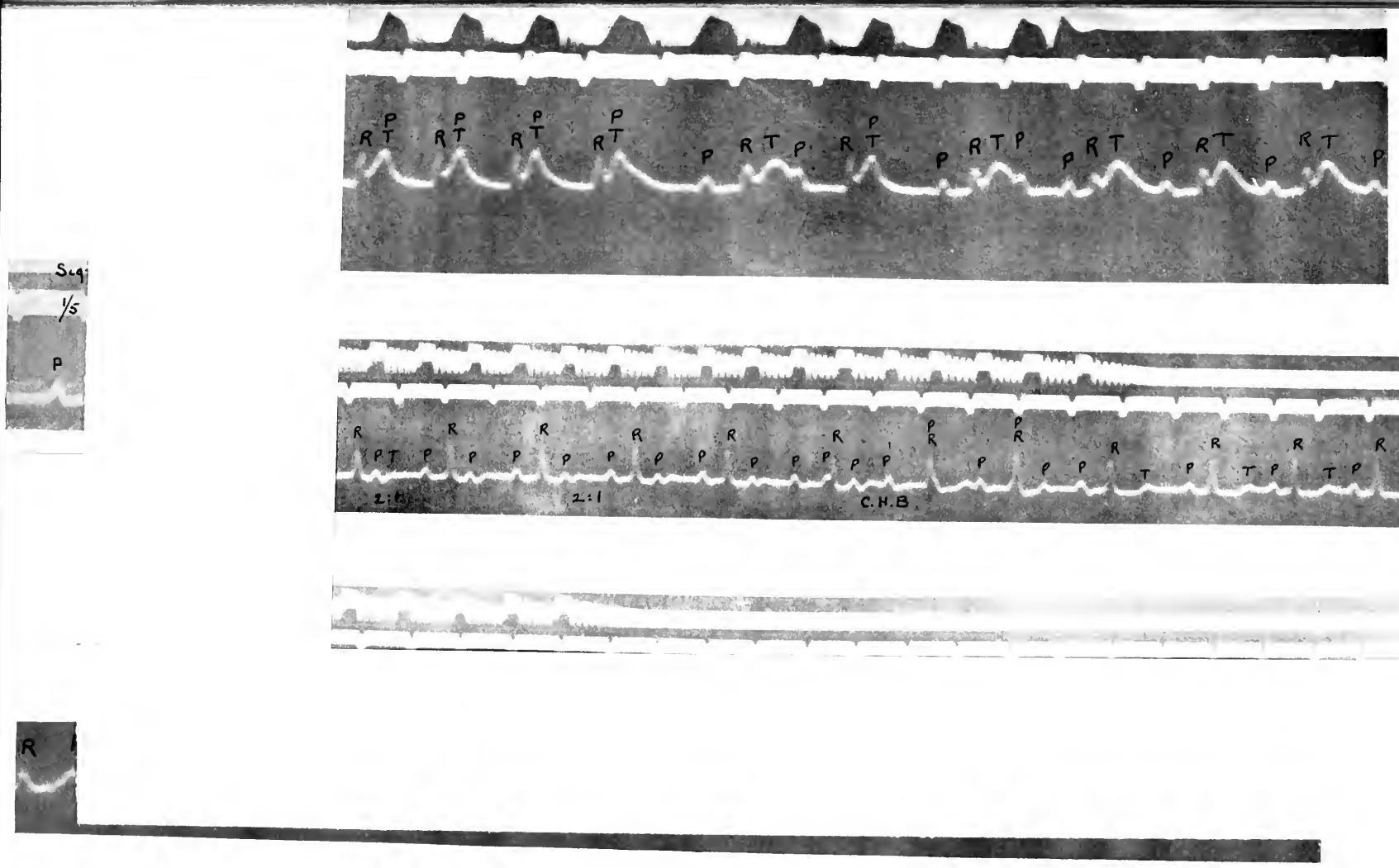


FIG. 9

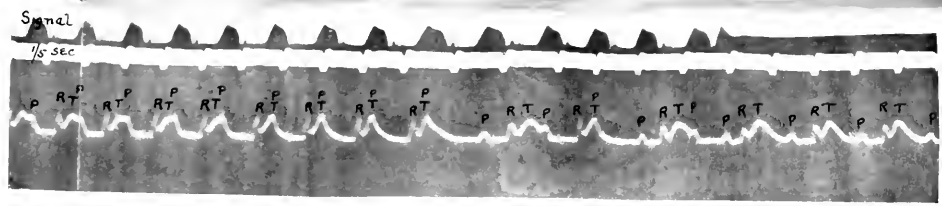


Fig. 1

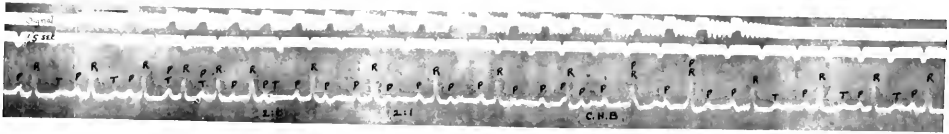


Fig. 2

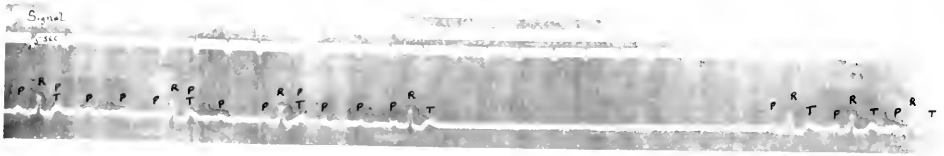


Fig. 3

Fig. 4

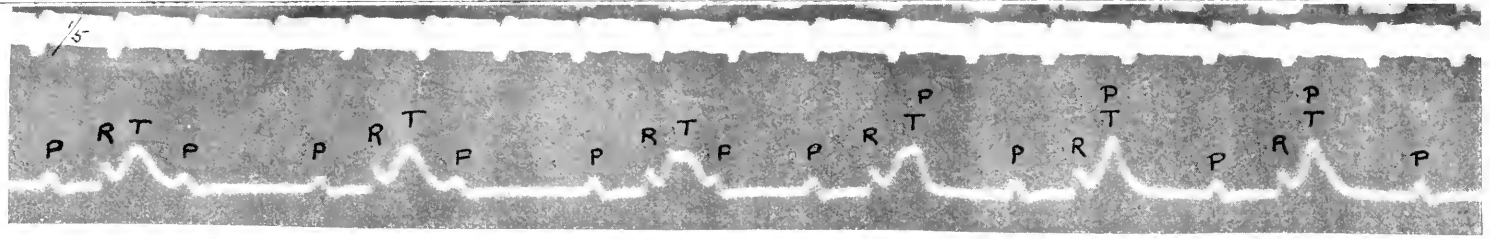
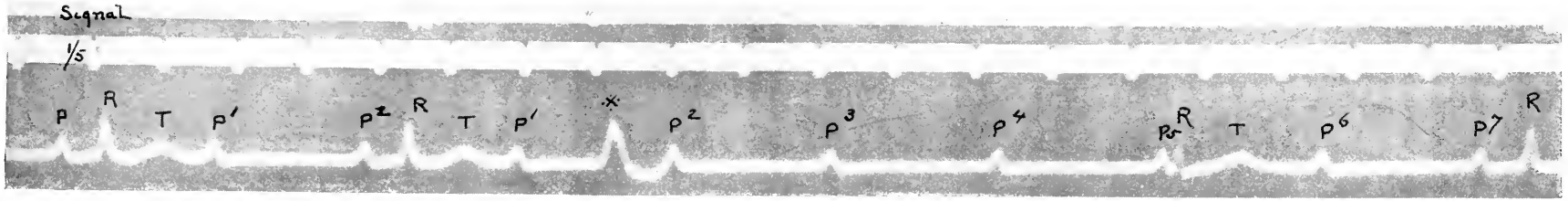

1/5
P R T P P R T P P R T P P R T P P R T P P R T P P R T P

FIG. 5


Signal
1/5
P R T P' P² R T P' * P² P³ P⁴ P⁵ R T P⁶ P⁷ R

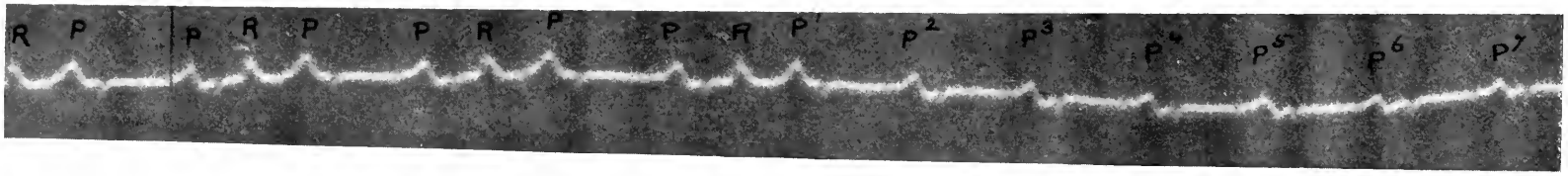
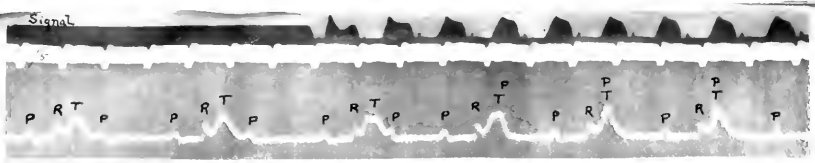
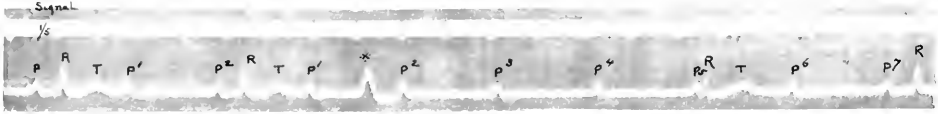
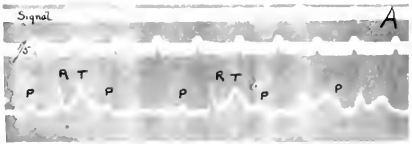
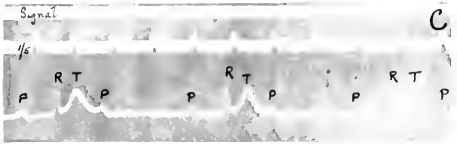

R P P R P P R P P R P' P² P³ P⁴ P⁵ P⁶ P⁷

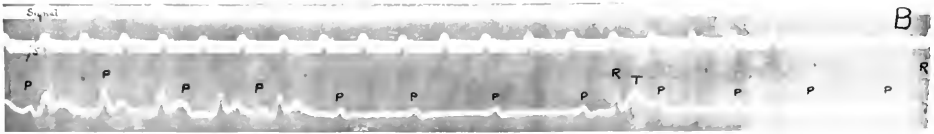
FIG. 9


Signal
P R T P
P R T P
P R T P
P R T P
P R T P
P R T P
P R T P


Signal
1/5
P R T P'
P2 R T P'
*
P2
P3
P4
R R T P6
P7 R


Signal
A
1/5
P R T P
P R T P
P


Signal
C
1/5
P R T P
P R T P
P R T P


Signal
B
1/5
P
P
P
P
P
P
P
P
R T P
P
P
P
R

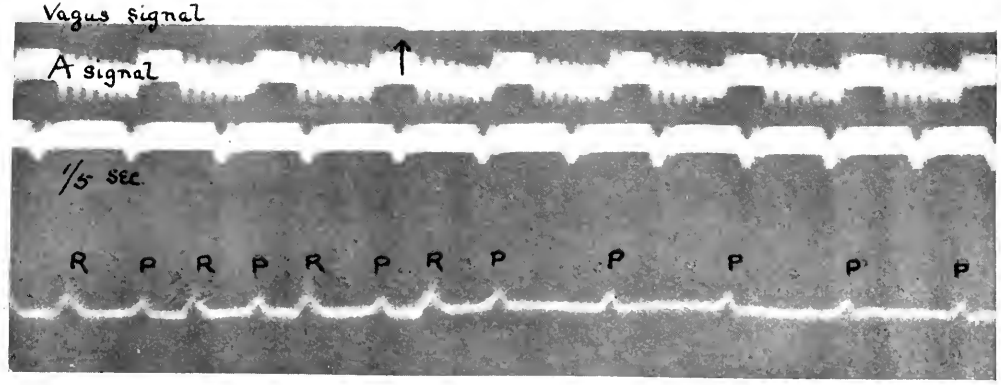

Vagus signal
A signal
1/5 sec.
R P R P R P R P P P P P

FIG. 8

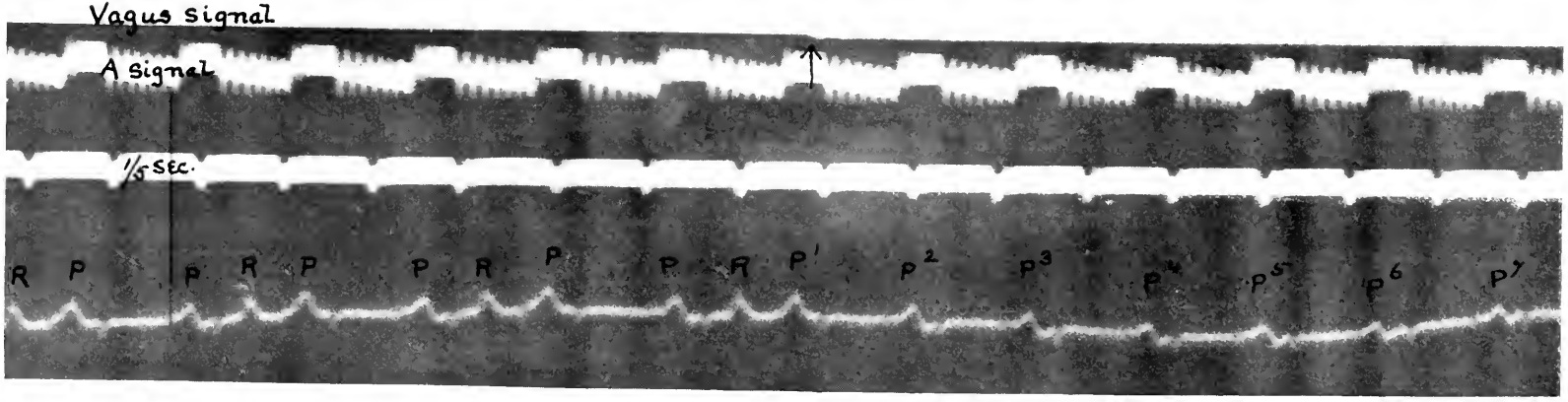

Vagus signal
A signal
1/5 sec.
R P P R P P R P P R P' P2 P3 P4 P5 P6 P7

FIG. 9

The effect of successive ventricular beats is often more pronounced. Induced ventricular tachycardia during the prolonged P–R stage may result in a temporary further prolongation of the P–R interval or in a temporary 2 : 1 heart-block at the cessation of stimulation. Again, the effect of a similar ventricular tachycardia during a period of 2 : 1 heart-block is manifested by the production of short periods of increased block at the termination of such tachycardia. This increased block may be a 3 : 1 heart-block, a 4 : 1 heart-block, or on rare occasions complete heart-block, lasting for a few cycles; each is followed by the reappearance of the original 2 : 1 rhythm which preceded stimulation (Fig. 7, *A*, *B*, and *C*).

In all these experiments it is noticeable that the degree of enhanced heart-block is largely dependent upon the length of the induced ventricular tachycardia. With short periods there may be no increase of the block, with longer periods it is almost invariable, and usually the block reaches a high grade.

It is obvious that induced ventricular beats have a distinct influence on the conduction of impulses from auricle to ventricle, when this conduction is primarily impaired by asphyxia. In none of the control experiments has there been any influence of this nature, so long as the P–R was of normal duration.

The question arises as to how this increase of heart-block as a result of induced ventricular beats is produced. The increase is in no way attributable to the steady progression of the grade of heart-block occurring during the asphyxial experiments. The temporary enhancement of heart-block gives place to a return to the original degree present directly prior to stimulation, in the great majority of the experiments.

In considering this question the effect of induced ventricular tachycardia upon the retrogression of impulses to the auricle is of importance. Successive and induced ventricular beats, following each other regularly and at a rate more than sufficient to outpace the normal auricular impulse formation, retrogress in control experiments from the third to the twenty-seventh cycle (usually between the fifth and the twelfth cycle). On the other hand, a prolongation of the P–R interval from, say, 0·08 sec. to 0·14 sec. absolutely prevents the occurrence of retrograde contraction. The same applies of course to higher grades of heart-block, i.e. 2 : 1 heart-block, 3 : 1 block, &c. (Fig. 7).

In brief, ventricular tachycardias occurring during the stage of heart-block are never retrograde; yet these same tachycardias bring about a striking increase in the degree of heart-block originally present (Fig. 7). The increase of heart-block, therefore, cannot be rationally attributed to fatigue of the *A–V* bundle as a result of its possible contraction in response to the impulses of the induced ventricular beats, for we have evidence that the upper portions of the junctional tissues are not affected by these tachycardias. It seems probable that the increased grade of heart-block is the result of fatigue of the lowest levels of the junctional tissues, perhaps of the arborizations of the main branches of the bundle. The actual level of the fatigue cannot be fixed.

The Effects of Vagus Stimulation upon partial Heart-Block.

In their clamp experiments, Erlanger and Hirschfelder state that stimulation of the vagus during periods of partial heart-block is not accompanied by an increase in the grade of the block. At a later date Erlanger writes, 'Stimulation of the vagus nerve sometimes causes a block to develop at the auriculo-ventricular junction of the normal heart. But on the other hand, stimulation of this nerve during partial heart-block may remove, or diminish the intensity of, the block.'

We have investigated the effects of vagal stimulation upon the partial heart-block of asphyxia, and find that the effect is very definite. The essential difficulty experienced by Erlanger lay in the fact that with the stimulation of the inhibitory nerves, the resultant slowing of the auricle complicated the reading, and rendered it difficult to ascertain the actual degree of change which occurred in the facility with which the impulses were transmitted. In the present experiments this difficulty has been obviated by maintaining a constant auricular rate with interrupted induced shocks. It is necessary to use a relatively high strength of current, for, during the heart-block stage and more especially during the period of vagal stimulation, the excitability of the auricle is markedly depressed. The actual electrical shocks consequently often appear upon the curves (Fig. 9). Stimulation of the vagus during the period when the P–R interval is prolonged produces a high grade of partial heart-block (Fig. 8). The same applies to stimulation during 2 : 1 phases of heart-block. The effect is almost immediate (Fig. 9). The next anticipated response of the ventricle is missed, and as a rule there is no further response until several auricular cycles have passed, subsequent to the termination of the vagal stimulation. The recovery is rapid, and usually that grade of heart-block appears which was present before the excitation of the vagus. On some occasions an over-recovery has been noted.

Summary.

The results of this investigation may be briefly stated as follows:—An increase of auricular rate during the heart-block caused by asphyxia increases the grade of heart-block. The observation is parallel with that made by Erlanger and Hirschfelder in their clamp experiments.

Single premature ventricular beats and ventricular tachycardias likewise produce an increase in the grade of a preceding asphyxial heart-block, but we find the increase to be more pronounced than Erlanger has stated it to be in his clamp experiments. A single premature ventricular contraction occurring just antecedent to an expected ventricular response may lead to a failure of three or more ventricular responses to auricle. Tachycardias of ventricular origin are usually succeeded by marked grades of increased block.

The increase in the degree of heart-block following single ventricular beats or ventricular tachycardia is brought about independently of the retrogression of the ventricular impulses to the auricle.

The heart-block of asphyxia reacts to certain interfering factors, such as auricular and ventricular tachycardia, in a similar manner to the heart-block produced by compression of the auriculo-ventricular bundle.

The partial heart-block of asphyxia is enhanced by stimulation of the vagus.

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2. Erlanger, *Amer. Journ. Physiol.*, 1906, xvi. 160.
3. Lewis and Mathison, *Heart*, Lond., 1910, ii. 47.
4. Roaf and Sherrington, *Quart. Journ. Exper. Physiol.*, Lond., 1910, iii. 209.
5. Sherrington, *Journ. Physiol.*, Camb., 1909, xxxviii. 381.

DESCRIPTION OF FIGURES.

PLATE 23, FIG. 1. ($\times \frac{9}{9.5}$ linear.) Cat XVI. Intact, chloroformed, and curarized. Vagi cut. An electrocardiographic curve, taken 1 min. 25 sec. after the onset of asphyxia, and at the end of a period of interrupted stimulation of the auricle. Before the onset of stimulation the P–R interval was of the same duration as that shown at the end of this figure; it was slightly prolonged. During the tachycardia it shows progressive increase, so that the auricular systole falls back further and further upon the preceding ventricular systole. In the terminal phases of stimulation, three responses are missed. At the actual cessation of stimulation, recovery is manifest. In this as in all the succeeding figures, the upper line represents the signal of induction shocks; the second line, $\frac{1}{5}$ sec.; the third, the electrocardiograms.

FIG. 2. ($\times \frac{9}{13.5}$ linear.) Cat XIX. Decapitated cat. 1 min. 45 sec. after the onset of asphyxia. A curve taken during the phase of prolongation of the P–R interval and showing the effect of interrupted induction shocks thrown into the auricular tissue. The prolonged P–R interval shows a further increase in the early phases of stimulation, and at the point marked in the curve passes into a 2:1 rhythm; at a further point marked in the curve dissociation appears. Complete recovery to a slightly prolonged P–R follows the cessation of stimulation.

FIG. 3. ($\times \frac{9}{13.5}$ linear.) A curve taken from the same animal some 40 sec. later. The auricle was stimulated during the prolonged P–R stage. The induction shocks produced a high grade of partial heart-block, and at their cessation a long period of 2 sec. occurred, during which the whole heart stood still. Complete recovery is shown in the last three cycles of this tracing. Such stoppage of the whole heart is but an occasional event.

FIG. 4. ($\times \frac{9}{13.5}$ linear.) Cat XVI. Intact, chloroformed, and curarized. Vagi cut. A record taken 1 min. 55 sec. later than Fig. 1 and from the same animal. The stimulation, during 2:1 heart-block, preceded the record and is not shown; the effects are manifested up to a point where the second ventricular beat occurs. The first and probably the second ventricular beats are ideo-ventricular. The last three cycles belong to a 2:1 period. The first two ventricular beats are considered ideo-ventricular on account of the variation in the shape of the ventricular complexes.

PLATE 24, FIG. 5. Cat XVI. Intact, chloroformed, and curarized. Vagi cut. 1 min. and 40 sec. after the onset of asphyxia. A curve taken during the earliest period of a phase of 2:1 heart-block, and showing the effect of a slight increase in the rate of the auricle, as a result of interrupted induction shocks applied to it. Where the 2:1 heart-block has been of but short duration, such slight increases of rate may not increase the apparent grade of heart-block, but may actually increase the ventricular rate, as in this instance. It does not necessarily follow that the grade of heart-block is decreased; there is every reason to believe that it may be increased at such times.

FIG. 6. ($\times \frac{9}{10}$ linear.) Cat XIII. Intact, chloroformed, and curarized. Vagi not divided. An electrocardiogram taken 1 min. 50 sec. after the beginning of asphyxiation, during the stage of 2:1 heart-block. The accompanying curve shows two cycles of the 2:1 heart-block, and at a point marked by an asterisk a premature beat is excited in the right ventricle by means of a single induction shock; the response to the excitation occurs at a point just preceding that at which the auricular contraction (P_2), to which a response is expected, falls. As a result of this abnormal ventricular contraction, the expected response of the ventricle to the succeeding auricular contraction is missed, and two additional auricular contractions, P_3 and P_4, take place without response. The first ventricular contraction is an escaped beat and it falls directly after P_5. There is no response to P_6, but there is to P_7; 2:1 rhythm is resumed. The effect of the induced ventricular contraction upon conduction is marked; it is more marked than usual, for in most instances a response of the ventricle would occur to P_4 or P_5.

FIG. 7. ($\times \frac{9}{11}$ linear.) Cat XXI. Decapitated cat. An electrocardiogram taken during a stage of 2:1 heart-block, and showing the effect of an induced ventricular tachycardia upon the transmission of impulses from auricle to ventricle. The first of the successive excitations falls in the refractory period of the ventricle; the second and third are effective and are shown in the first strip (7*A*). The ventricular tachycardia is continued from this point through twenty-three cycles; the nineteenth to twenty-third cycles are shown in the second strip (7*B*). It is to be observed that throughout the whole of this tachycardia stage the ventricular impulses are never retrogressive to the auricle. At the cessation of stimulation, two clear cycles of 4:1 rhythm are seen; three additional cycles of the same kind are omitted. The subsequent return to 2:1 heart-block is shown in the third strip (7*C*). The figure illustrates the increase of a pre-existing heart-block as a result of ventricular tachycardia, none of the contractions of which are transmitted to the auricle.

PLATE 25, FIG. 8. Cat XXV. Intact, chloroformed, and curarized. Vagi intact. A curve taken during the stage in which the P–R interval is prolonged. An additional record, that of vagal stimulation, is seen in the uppermost line in this figure, and in Fig. 9. The auricle is responding throughout to regular induction shocks; its rate is therefore constant. The vagus was stimulated at the point marked by the arrow, and from this point onwards the ventricle fails to respond.

FIG. 9. A similar curve from the same animal as Fig. 8, showing the effect of vagal stimulation during a phase of 2:1 heart-block. The vagal stimulation commenced at the point marked by the arrow, and from this point onwards isolated auricular beats, P_1, P_2, P_3, &c., continued. The vagal stimulation continued up to P_{15}. The first response of the ventricle was seen at P_{20}, the second at P_{25}, the third at P_{28}, and from this point 2:1 heart-block was maintained.

Journal Physiology, Vol. XLII.
[*From the Proceedings of the Physiological Society*, Jan. 21, 1911.]

Sudden death under light chloroform anaesthesia. By A. G. Levy.

(*Preliminary Communication.*)

From the Research Laboratories of the Medical School, University College Hospital.

The sudden death of animals under properly established chloroform anæsthesia is a comparatively rare event, but I have had experience of nine cases of this kind in cats in the course of experiments in which the blood-pressure was being observed.

These deaths occurred very suddenly, but I was fortunate in obtaining two complete tracings in which both respiration and blood-pressure were being recorded at the moment of the event. There is however sufficient evidence from the remaining incomplete records to show that the cases resemble one another in important particulars. The animals were all efficiently anæsthetised, but the anæsthesia was of a comparatively light description, the percentage of vapour administered ranging from 0·5 % up to 1·5 %. The heart failure was absolutely sudden, the blood-pressure falling precipitately without evidence of heart beats, and although an attempt at recovery might occur, especially when the experiment was being conducted under artificial respiration, the heart ultimately failed again in an exactly similar fashion. It is as a rule impossible to restore these animals to life, but in one other case, after an apparently similar fall of pressure, the heart did spontaneously and permanently recover following the re-establishment of natural respiration.

The blood-pressure tracing which immediately precedes the collapse is uniform in character, the pressure being, for chloroform anæsthesia, high or fairly high, 89 mm. being the lowest and 180 mm. the highest recorded, and there is generally some evidence of a slight preterminal rise. The heart beat is always rapid, from 250 to 300 per minute, the individual beats being small in amplitude, and as registered by the mercury manometer, frequently wholly or partially indistinguishable. The mean pressure shows frequent small and irregular fluctuations which have no relation to respiratory movements, and is often compli-

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cated by occasional rapid small dips of pressure. This form of tracing is not uncommon in cats under light chloroform anæsthesia and is illustrated in Fig. 1.

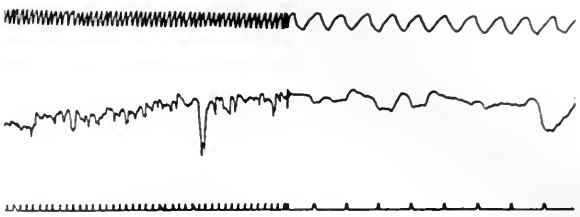

Fig. 1. Blood-pressure tracing of cat under light chloroform anæsthesia. Upper tracing respiratory. Time marked in seconds. In the second half the kymograph is working at a quick rate and in this part the individual pulsations can just be discerned. Pulse rate about 300 per minute. Mercury manometer.

The respiratory tracing when recorded, showed, after the heart had stopped, a few powerful convulsive gasps, and finally ceased, in one case in 12″ and in another in 18″. The respiration was always subject to recovery either spontaneous or from artificial means.

Illustrative Cases.

1. A vigorous cat was kept anæsthetised under 1·2 % chloroform with b.p. = 150 mm. Hg. Ligature of both carotids caused a rise of 18 mm., pulse rate 276 per minute. On reducing the chloroform to 0·5 % the pressure rose to 180 mm. and then the manometer float was seen to fall suddenly to zero, the kymograph not recording at the moment. The breathing ceased shortly after the fall of pressure, but recovered under artificial respiration. The heart beat could not be restored. The chloroform was administered on the "ad plenum" system, without tracheotomy.

2. Artificial respiration. Perflation of lungs with 0·5 % CHClg. One vagus cut. Stimulation of median nerve caused a slight rise of blood-pressure (highest point 110 mm. Hg) followed by a sudden profound fall. There was after an interval a sustained effort at recovery followed by a second sudden and permanent fall. The artificial respiration was continued until the end.

3. A vigorous cat was slowly anæsthetised by chloroform on a mask, it was then tracheotomised, and anæsthesia maintained by percentage chloroform administration by the "ad plenum" method.

The animal was never at any time deeply under, the corneal reflex being active up to the end. Chloroform 2 % was given for a short period and then a rubber bag containing 1·5 % CHClg was attached to the trachea tube. This was followed by sudden heart failure 55″ later, succeeded in another 18″ by cessation of respiration (see Fig. 2). B.p. just before death = 137 mm. The contents of the bag at the moment of death were analysed and found to contain 1·17 % CO_2 and 20·2 % O_2. The procedure is given in full, but it does not appear to have been the exciting cause of death.

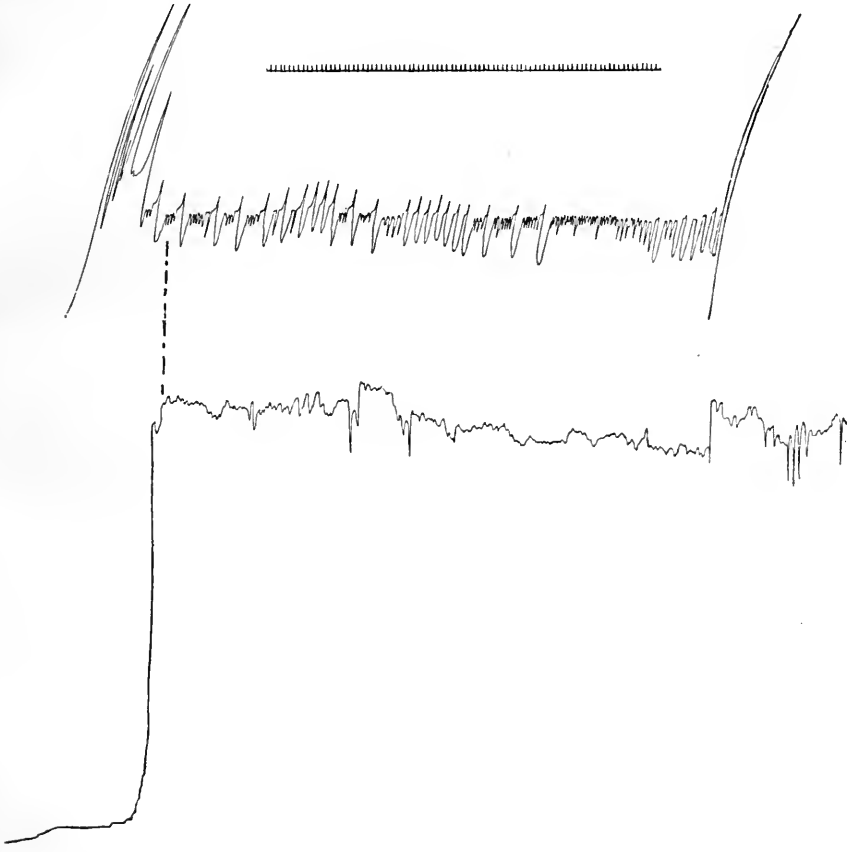

Fig. 2. Tracing illustrating sudden death, Case No. 2. Read from right to left. The interrupted vertical line indicates synchronous points in respirations and b.p. tracing. Time in seconds.

4. Artificial respiration. Both vagi cut. Sudden death followed a rise of pressure subsequent to the administration of CO_2. Chloroform at the moment of death = 1·2 %. Highest b.p. 108 mm. Hg.

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Professor Cushny kindly inspected some of my records, and acting on his suggestion, I sought for fibrillation of the ventricles in subsequent cases. In each of these, three in number, I found the ventricles dilated and fibrillating, with complete absence of pulsation. The auricles were pulsating feebly and continued to do so for some time.

The impression I gained from a review of all the cases was that the heart, under light chloroform administration, may become incapable of accommodation to vascular strain, and this view has received some confirmation from the results of the intravenous injection of adrenalin chloride, this proving almost invariably fatal from sudden heart failure when the anæsthesia was of a light description (Fig. 3 B). The tracing is remarkably similar to those of the spontaneous deaths previously described, the respiration ceasing however somewhat later.

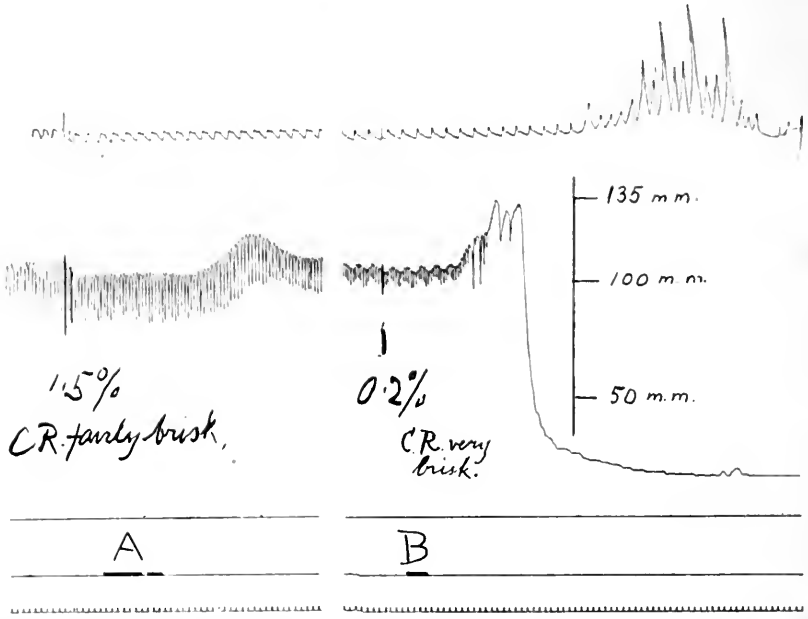


Fig. 3. Intravenous injection of 0·03 mgm. Takamine at the signal marks A and B. During the gap in the tracing 0·5% chloroform was administered. The heart beats in the final portion of the tracing are very small, barely visible. Time in seconds. C. R. = corneal reflex.

Details of Experiments. Adrenalin chloride was injected into the saphenous vein when the chloroform was at 1% or less, and the corneal reflex active. The dose of adrenalin generally given was 0·03 mgm. in a 1 m. 20,000 dilution. In thirteen cats out of fifteen sudden

collapse followed the rise of blood-pressure. In one case the heart recovered permanently, and in one other it recommenced to beat whilst the chest was being opened. In all other cases the breathing was restored but not the heart. In every case of death the ventricles were dilated and fibrillating, the auricles still pulsating. When the chest was opened immediately after death the auricles also might be seen fibrillating but soon recovering a regular beat.

Section of both vagi together with the subcutaneous injection of 0·065 mgm. of atropine sulphate did not protect against death. Full chloroform anæsthesia appears to be absolutely protective. (Fig. 3 A.) I have not so far succeeded in obtaining this reaction under ether anæsthesia either light or deep.

It is evident that the presence of some such special factor as light chloroform anæsthesia is essential for the production of sudden collapse from adrenalin, for the previously recorded instances are astonishingly few. Oliver and Schäfer[1] met with a single case only in a dog under chloroform, atropine, and morphia, and noted that the heart passed into a state of fibrillary contraction. Elliott[2] had a few mishaps of this nature in dogs, the anæsthetic not being specifically mentioned. I have not met with any previous record of such an occurrence in the cat. It would appear therefore that the condition of the heart under the influence of low percentages of chloroform requires investigation.

[1] *Journ. of Physiol.* XVIII.
[2] *Journ. of Physiol.* XXXII.

Working under the tenure of a Beit Memorial Research Fellowship.

NOTES UPON ALTERNATION OF THE HEART

By THOMAS LEWIS[1]

(From University College Medical School)

With Plate 22

Amongst the several affections of its mechanism to which the human heart is subject, none perhaps is less understood than alternation of the strength of its contractions. A great many observations have been made in regard to it, but the explanation of its production is still wrapped in obscurity.

During the course of a systematic investigation of cardiac irregularities, clinical and experimental, I have met with heart alternation in slight and marked degree on many occasions. From a number of observations a few, hitherto undescribed, have been selected for publication.

Heart alternation occurs under two circumstances. It is seen when the cardiac muscle is not of necessity altered structurally, as an accompaniment of great acceleration of the rate of rhythm. It is also found when the pulse is of normal rate, and under such circumstances the muscle is either markedly degenerate or the heart shows evidence of embarrassment as a result of poisoning or some other factor.

The observations now published are drawn from the first group.

Divergent Alternation.

In studying the effect of ligation of the coronary arteries, it was found that an obstruction of one or the other is usually followed by the appearance of rapid and new rhythms arising in the ventricle; and a detailed account of such rhythms will be found in another place (3). Suffice it to say that the ventricular rhythm dominates that of all the cardiac chamber; and that if the heart rate is greatly increased, alternation frequently appears. Examples of the curves obtained under these conditions are shown in Figs. 1 and 2. The four tracings of Figs. 1 and 2 were each obtained in similar manner. The uppermost curve in each is a ventricular myocardiograph, taken with a modification of Roy and Adami's instrument; the points of attachment were transversely across the centre of the heart. The second curve in each is a similar record from the right auricle. The third curve is a carotid pressure tracing, taken with a Hürthle manometer.

In a recent paper Hering has published simultaneous apex and radial curves from the dog and from a clinical case, which appear to demonstrate that, when alternation in excursion in both is manifested, the larger excursion in one

[1] Working under the tenure of a Beit Memorial Research Fellowship.

may be found to correspond to the smaller excursion in the other. The fact that the large apical curve may correspond to the smaller radial beat seems such a remarkable phenomenon, that, regarded as an expression of the relationship of the strength of ventricular contraction and the amplitude of the corresponding arterial curve, it can hardly meet with acceptance in the absence of confirmatory and more direct evidence. This evidence is provided by the three accompanying curves (Fig. 1). The curves represent a paroxysm of regular tachycardia in which the auricle is responding to the ventricle. Attention is drawn to the fact that in these curves the systoles of the ventricle (above) and of the auricle (below) are represented by downstrokes. They illustrate the changed relationship which may be found in ventricular, auricular, and carotid curves within short spaces of time. A few seconds intervene between each strip. In the first curve the large ventricular beat corresponds to the large auricular beat and to the large carotid upstroke. In the second curve the large ventricular beat corresponds to the large auricular and to the small carotid beat. In the third curve the large ventricular beat corresponds to the small auricular beat and to the large carotid beat.

It is shown, therefore, that the excursion of the arterial curve, when alternation is present, is not necessarily associated with parallel alternation in the amplitude of the ventricular muscle excursion, and that in one and other the alternation may be divergent. The simultaneous alternation in the auricle is of special interest. It is clearly shown to be independent of the ventricular alternation by a comparison of the first two with the last curve, for in the first two curves the auricular and ventricular alternations run with parallelism, while in the last they are divergent. Now if the exact relationship of the auricular and ventricular systoles be compared in any one of these curves it will be found that the auricular systole commences a trifle before the beginning of the diastole of the ventricular cycle to which it belongs (and to the contraction of which it is a response), and that it extends well into the said diastole. In brief, the auricular systoles are efficient in that they aid the filling of the ventricle. We have an immediate and I believe helpful clue to the appearance of divergent alternation in ventricle and carotid in the middle curve, for in this tracing, as opposed to the first, the auricular alternation is marked in its degree. The strong carotid pulsation is the result of the weak ventricular contraction, but the efficiency of the latter is reinforced by the preceding strong auricular contraction; similarly the small carotid pulsation is the outcome of the strong ventricular contraction, but the efficiency of the latter is embarrassed by the relatively small influx of blood as a result of the preceding weak auricular contraction. A comparison of the middle and right-hand curves (Fig. 1) will show that the ventricular excursion is of equal extent in each. The auricular and carotid alternations taken together are also divergent in each; but in the one instance the divergent auricular alternation increases the carotid alternation (right-hand curve), while in the other it diminishes it (middle curve).

The explanation offered of the curious anomaly presented by the middle

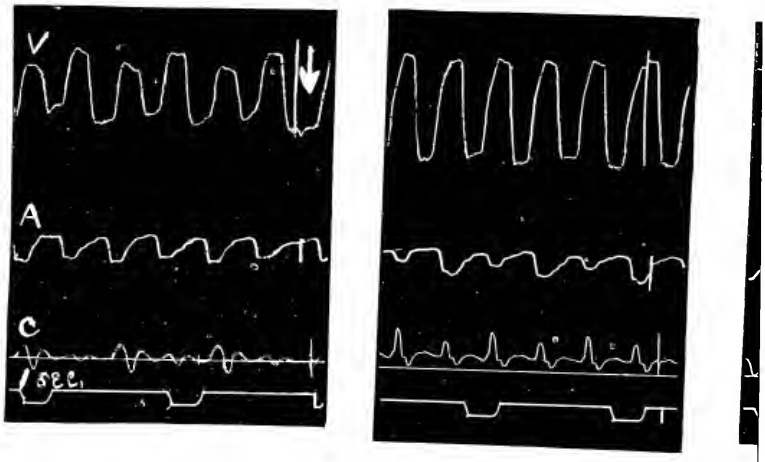
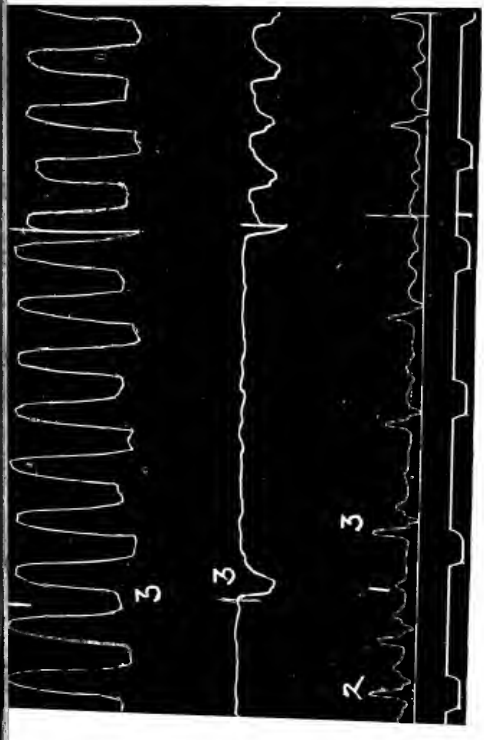


FIG. 1



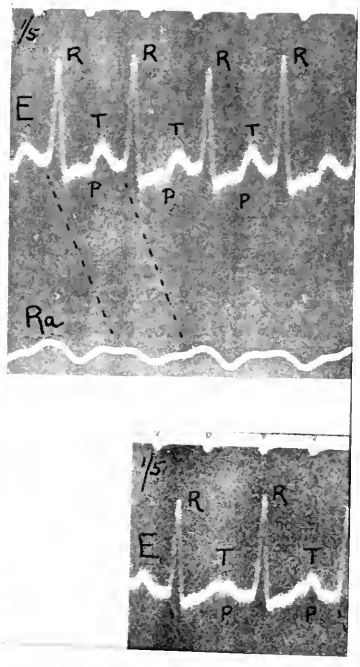


FIG. 2

[2] It should be stated that the auricular myocardiogram was obtained from the right auricle, and that it is assumed that alternation was also present in the left.

Fig. 1

Fig. 2

figure, namely, divergence of ventricular and carotid alternation, is strongly supported by further observation upon the same animal (the whole series of curves was obtained within a space of three minutes, and they are given in the order of their occurrence). At the commencement and ending of this figure (Fig. 2), strips of alternation are shown in which the occurrences are similar to those seen in Fig. 1 (right-hand curve). Over the central portion of the strip the vagus was stimulated; the ventricle is beating in response to inherent impulse formation, and the sole effect of the vagus excitation, in this instance, is the temporary suspension of auricular activity. But at three points an auricular response to ventricle is recorded, and the effects of these three beats are strikingly shown in the carotid curve. The first escaped auricular beat (*1*) falls *during* a *weak* ventricular contraction (*1*), and its influence is felt by the succeeding strong carotid pulsation (*1*), which is markedly exaggerated. The next auricular contraction (*2*) is a response to a *strong* ventricular systole (*2*), with which it falls; as a consequence it causes a temporary abolition of alternation in the carotid, by increasing the amplitude of an expected weak carotid beat (marked *2*). The third response shows similar time relationships to the first, and gives rise to similar carotid changes; but it may be noted that just as the third auricular beat is weaker than the first, so the third carotid beat is weaker than the first.

As a result of these observations, therefore, it seems clear that certain instances of divergent alternation in ventricle and carotid may be the result of simultaneous alternation in the auricle.[2] A curve has been published by Volhard which supports this view. He gives simultaneous curves from jugular, apex, and radial in a patient exhibiting alternation. In his figure (Fig. 1) the larger apical curve corresponds to the smaller radial beat, but alternation is also seen in the amplitude of the *a* waves in the jugular, and in this instance the small radial beat is preceded by the small *a* wave.

The Electrocardiogram in Clinical Alternation.

This note upon heart alternation may be concluded by a brief description of some electrocardiographic curves obtained from a patient, the subject of auricular tachycardia, whose case has been otherwise fully described in a previous communication (3). The facts in regard to the electric curves in alternation are already known as a result of experimentation (1 and 2), and their publication is chiefly demanded because it brings the clinical and experimental appearances more closely into line.

Each of the accompanying photographs portrays an electrocardiogram and radial curve from the same patient. All are from paroxysmal periods, and the abnormal (in this case inverted) *P* variation is seen superimposed upon *T*, the second ventricular variation. It notches it in a downward direction, occurring at the commencement of *T* in Fig. 3, I and III, and near the apex of *T* in

[2] It should be stated that the auricular myocardiogram was obtained from the right auricle, and that it is assumed that alternation was also present in the left.

Fig. 3, II. It will suffice if the chief points demonstrated by the curves are noted. The shape of each ventricular complex shows it to result from a contraction of supraventricular origin. The distinction between alternation and premature ventricular contractions arising late in the cycle is clearly defined. From beat to beat the curves are similar in their general conformation; they fail to support the view expressed by Hering that alternation may result from intraventricular heart-block, for under such circumstances a notable change in the general outline from beat to beat would be expected.

The alternate beats show only slight quantitative changes in the several peaks. The short *R* is usually accompanied by a slightly exaggerated *T* (Fig. 3, I), though it may be accompanied by a diminished *T* (Fig. 3, II), or by a *T* in which no change is detected.

The relationship to alternation in the arterial curve is equally variable and equally obscure. In the beginning of Fig. 3, I, alternation in *R* runs parallel with that of the pulse for the first four beats. That is to say, the tall *R* corresponds to the slightly taller radial beat. In the last beats of the same photograph the trace of alternation in the pulse vanishes, while the alternation of *R* increases somewhat. Alternation of the pulse to extinction is shown in the next figure, and the complex composed of a high *R* and a high *T* is associated with absent radial pulsation. In the last figure alternation is well defined in the radial curve, while it is not discoverable in the electrocardiogram.

The explanation of these phenomena is unknown, and a discussion of them is impossible at the present time.

Conclusions.

1. Divergent alternation of ventricle and carotid, a condition in which the large ventricular contraction corresponds to the small carotid upstroke, is encountered experimentally. The divergence is due in some instances to simultaneous alternation of the auricle.

2. The electrocardiographic curves obtained in clinical heart alternation are similar to those obtained experimentally; there is a divergence between the heights of *R* and *T* and the amplitude of the radial upstrokes. These facts demonstrate the identity of the clinical and experimental conditions.

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OBSERVATIONS ON THE OCCURRENCE OF FLUID IN THE ABDOMINAL CAVITY IN PREGNANT RABBITS.

BY

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and

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THE presence of free fluid in the abdominal cavity of the pregnant rabbit has been noticed in the course of research by several observers, but as far as we are aware no special observations have been made with regard to the nature of the fluid present nor to the possible cause of its occurrence. It has occurred to us that some such observations may be of value, especially in relation to the work done by one of us (C. B.) on the pathology of cardiac dropsy.

Relative Frequency.—The relative frequency of free fluid in the peritoneal cavity has been estimated in a series of pregnant and non-pregnant animals:

(*a*) Non-pregnant: Ten non-pregnant animals were examined, 4 males and 6 females, and although the intestines were moist in all cases, in only 2 was a measurable quantity of free fluid obtained, and in these 2 cases (1 male and 1 female) the quantity was very small, as indicated below.

(*b*) Pregnant: In 16 pregnant animals examined, we only failed in 2 cases to obtain a measurable quantity of fluid. This gives the following percentages of cases with free fluid:

(*a*) Non-pregnant, 20 per cent. (probably is much smaller).
(*b*) Pregnant, 87.5 per cent.

Distribution.—The presence of free fluid in the pleural cavity was noted in 3 cases in pregnant animals and in no case in a non-pregnant. In the pericardium a small quantity of fluid was generally found in all cases. In no case was subcutaneous oedema present.

Amount of Fluid Present in the Abdomen.—(*a*) Non-pregnant: In the 2 cases occurring in the series of 10 non-pregnant animals examined the quantity of fluid amounted to 2 c cm. and 3 c.cm. respectively.

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(*b*) Pregnant.—In the series of 16 animals, 14 had fluid in quantity varying from 1.15 c.cm. to 25 c cm.

The series is as follows:

I. 1.15 c.cm.	VII. 3.50 c.cm.	XII. 2.50 c.cm.
II. 14.50 c.cm.	VIII. 2.50 c.cm.	XIII. 2.00 c.cm.
III. 9.00 c.cm.	IX. 3.50 c.cm.	XIV. 1.50 c.cm.
IV. *Nil.*	X. 8.00 c.cm.	XV. 25.00 c.cm.
V. 3.00 c.cm.	XI. 5.00 c.cm.	XVI. 15.00 c.cm.
VI. *Nil.*		

We feel justified from these figures in concluding that the presence of free fluid in the abdomen is a more or less general occurrence in pregnant rabbits and not merely a coincidence.

Blood Pressure.—We have examined a series of non-pregnant and pregnant animals with a view to ascertain whether any blood pressure changes were to be noted in animals with free abdominal fluid.

Technique: Anaesthesia.—Ether was used in all cases, anaesthesia being induced with a mask. Tracheotomy was then performed, and the administration of ether continued through an apparatus attached to the artificial respiration pump. Special care was taken to imitate the natural respirations of the animals by careful regulation of the pump, a free outlet of air being provided.

Position.—The animals were fixed to a board in the supine position, care being taken to tie them down loosely so as not to interfere with the venous flow. The head was slightly raised on a small board, the same board being used for all experiments.

Method of taking Blood Pressures.—The following routine was followed in all the cases after the first two or three. First the pressure was taken in the right carotid artery with an ordinary mercurial U tube manometer; then the blood pressure in the left external jugular was taken by passing a cannula down the large auricular vein until the mouth of the cannula came to lie flush with the wall of the jugular vein without obstructing the flow of blood in that vessel. The cannula was then connected with a manometer containing a solution of $MgSO_4$ (specific gravity 1046) and the pressure in millimetres recorded; the height of the vein above the table on which the manometer stood was then measured and deducted from the pressure recorded. The pressure in the common iliac vein was now recorded in a similar manner by passing a cannula up the femoral vein. At the end of each experiment the pressure in the left carotid artery was again taken.

In a few cases we attempted to take the pressure in the portal vein, but we found this rather difficult, and

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4. Volhard, *Münch. med. Wochenschr.*, 1905, lii. 1. 590.

therefore decided to work it out in a separate series of animals.

The results obtained are indicated below:

(a) Non-pregnant Animals.

No. of Experiment.	Sex.	Carotid Artery B. pressure in mm. Hg.	Jugular Vein in mm. $MgSO_4$ Sol.	Iliac Vein in mm. $MgSO_4$ Sol.	Fluid in Abdomen in c.cm.
1	M.	90	55	83	—
2	M.	60	60	Not obtained	—
3	F.	110	50	85	—
4	F.	58	35	Not obtained	2 00
5	F.	70	37	85	—
6	F.	75	20	120	—
7	M.	65	50	89	—
8	M.	80	45	115	3.00
9	F.	80	39	Not obtained	—
10	F.	77	51	112	—

(b) Pregnant Animals.

No. of Experiment.	Carotid Artery in mm. Hg	Jugular Vein in mm. $MgSO_4$ Sol.	Iliac Vein in mm. $MgSO_4$ Sol.	Fluid in Abdomen in c.cm.
I	70	42	125	1.15
II	90	50	75	14.50
III	50	56	88	9.00
IV	50	38	74	*Nil.*
V	90	54	Not obtained	3.00
VI	90	70	96	*Nil.*
VII	52	53	83	3.50
VIII	70	62	110	2 50

It will be seen from the foregoing that the difference in blood pressure in the two cases is not appreciable, and we feel justified in assuming that there are no pressure changes in the peripheral circulation in the animals with ascites. We believe the same to be true of the portal circulation, but our experiments have not so far enabled us to make a definite statement on this point.

Composition of Fluid in the Abdominal Cavity.—We have examined the blood, the fluid found in the abdominal cavity, and in some cases also the chyle, for total solids.

anæsthesia.

Technique.—The blood serum was obtained by bleeding the animals from the carotid artery into dried glass tubes, allowing the blood to clot, and centrifugalizing. A portion of the serum was weighed in a dry glass capsule, dried at 60° C., and finally heated to 108° C. and weighed again.

The fluid from the abdominal cavity, which was a practically colourless fluid, was collected into similar tubes with a pipette and allowed to coagulate spontaneously, which it did in all cases in about half an hour. It was then centrifugalized and treated in the same way as the blood serum.

In order to obtain the abdominal fluid for analysis we used only animals in which the blood pressure had not been taken, in order to avoid the possible error of producing ascites by introducing $MgSO_4$ solution into the circulation.

Considerable difficulty was experienced in obtaining chyle in sufficient quantity for estimating the total solids; we first attempted to obtain it from the subclavian vein after ligature of the surrounding blood vessels, but failed to obtain undiluted chyle. We also found isolation of the thoracic duct unsatisfactory, and finally obtained the chyle by opening the receptaculum chyli, after all the abdominal fluid had been removed and the animal bled to death.

The examination of the various fluids for their total solid contents gave the following results:

No. of Experiment	Blood Serum. Total Solids per Cent.	Abdominal Fluid.		Chyle. Total Solids per Cent.
		Amt. c.cm.	Total Solids per Cent.	
IX	6.896	3.50	2.741	—
X	6.324	8.00	2.349	—
XI	7.352	5.00	3.978	—
XII	5.866	2.50	2.254	—
XIII	7.691	2.00	3.115	8.629
XIV	6.738	1.50	4.220	3.738
XV	7.509	25.00	3.226	6.122
XVI	7.433	15.00	4.567	3.550

These figures closely correspond with those obtained in the case of heart disease in the human subject.

4. Volhard, *Münch. med. Wochenschr.*, 1905, lii. 1. 590.

We have not yet had the opportunity of comparing the results thus obtained with fluid obtained from non-pregnant animals, as we used the only two cases that have come under our notice for blood-pressure experiments.

The type of dropsy in these animals, therefore, corresponds more closely to that of heart disease than to that seen in disease of the kidney or in hepatic cirrhosis, in both of which conditions the oedema fluid contains much less solid matter.

This conclusion is not at variance with the pathology of cardiac ascites, because, as shown by one of us,[1] in that condition there may be no changes of pressure in the peripheral circulation.

REFERENCE.

[1] Bolton: (*a*) *Journal of Pathology and Bacteriology*, August, 1903; (*b*) *Proceedings of the Royal Society*, B., vol. lxxix, 1907; (*c*) *Journal of Pathology and Bacteriology*, vol. xiv, 1909.

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ASPHYXIA UNDER CHLOROFORM.

By A. Goodman Levy.[1]

This research was undertaken to investigate the effect of asphyxia in animals under the influence of chloroform in view of a prevalent tendency to attribute a lethal importance to a condition of partial asphyxia induced accidentally in the course of chloroform anæsthesia and termed "intercurrent asphyxia." The apparent importance of this condition is emphasized in the Report of the Hyderabad Commission [15], and passing references to it are found in papers upon chloroform by Embley [3], and by Schäfer and Scharlieb [17]. Sherrington and Sowton [19] found that chloroform depressed the isolated mammalian heart more when it was perfused in a saline solution under asyphyxial conditions than when the solution was oxygenated; this work, as the authors state, lacks controls and completion. F. W. Hewitt [8] has been a frequent exponent, from a clinical standpoint, of this view, and more recently R. Gill [7] has published a treatise on the subject of a partial asphyxia which he infers is inherent to chloroform inhalation.[2] With the exception of Sherrington and Sowton's work no systematic investigation of the subject appears to have been undertaken, but general surmise has led to an extensive adoption of a plan of administering oxygen with chloroform for clinical purposes.

[1] From the Research Laboratories, University College Hospital Medical School.

[2] Since writing the above, Gardner and Buckmaster [6] have shown that the oxygen content of cats' blood may be reduced to 60 per cent. of the normal in full chloroform anæsthesia.

There would appear to be good reasons for taking this subject into serious consideration, for it is generally accepted that asphyxia has an exciting effect upon the cardio-inhibitory centre, and as it is also held that chloroform itself determines its activity (Embley [3], McWilliam [12], &c.), it might be anticipated that the combined action of chloroform and asphyxia would result in a strongly reinforced inhibitory action.

In the course of my experiments it became evident that it was necessary to adopt a standard of comparison, and this was afforded by parallel experiments conducted under the influence of ether. It is an obvious fact, judging by clinical experience, that intercurrent asphyxia under ether, however objectionable, is not of any serious importance, at any rate in so far as it affects the occurrence of sudden death. A degree of cyanosis (frequently, in fact, considerable) accompanies the administration of ether by the usual "closed" method, and has even been regarded (mistakenly so, as is now known) as a necessary adjunct, yet notwithstanding this it has never been suggested that such rare accidents as occur under ether may be attributable to intercurrent asphyxia. Further, ether does not of itself appear to excite the cardio-inhibitory centre, and therefore experimental asphyxia under ether provides a good standard by which to judge of experimental asphyxia under chloroform.

This investigation has been resolved into two separate lines of research, considered here in separate sections.

Section A.—Heart Failure from Reflex Cardiac Inhibition.

The influence of chloroform upon the cardio-inhibitory reflex is similar to that which it exercises upon most other reflexes—i.e., progressive depth of anæsthesia progressively obscures the reflex. This fact was pointed out by François-Franck [4], and I have frequently confirmed his observation under the graduated administration of chloroform. The influence of asphyxia alone upon the cardio-inhibitory reflex has been studied also by François-Franck [5], who found that the cardio-inhibitory reflex induced by stimulating the infra-orbital nerve is abolished in an advanced stage of asphyxia. In this connexion also attention must be drawn to the observation of C. S. Sherrington [18] that asphyxia in the spinal dog first intensifies limb reflexes and finally suppresses them.

To study the combined effect of chloroform and asphyxia upon the cardio-inhibitory reflex I proceeded as follows: The animal, a cat, was tracheotomized under chloroform anæsthesia. The distal end of the tracheotomy tube was arranged to lie in a narrow-necked bottle into which a continuous current of air mixed with chloroform was pumped in excess of the animal's respiratory requirements. The percentage of vapour was carefully regulated in percentage terms. The blood-pressure was registered by a mercurial manometer connected with a carotid artery. The respiration was recorded from the thoracic respiratory movements, for the respirations are mainly abdominal in the cat under normal chloroform anæsthesia and are little affected by asphyxia, whereas the thoracic respirations, normally very slight, are intensely exaggerated by asphyxia and afford a very graphic index of the progress of the latter. The vagal reflex was produced by stimulation of the central end of a cut vagus nerve with a faradic current, the other vagus remaining intact. It frequently happens that the inhibitory element of this complex reflex is unobtainable or insufficiently marked, but it is more constantly obtained from the vagus than from the superior laryngeal nerve; the superior laryngeal reflex is furthermore frequently evanescent. When the inhibitory reflex is obtainable very similar results follow consecutive stimulations of the same intensity, provided the anæsthesia is maintained at an unaltered level during the intervals.

Asphyxia was produced by causing the animal to respire a confined atmosphere. A rubber bag was partially inflated with the same chloroform atmosphere that the animal had been inhaling for some time previously, and was attached to the trachea tube. The extent of inflation was made consistent with the desired rapidity of the asphyxial process. The vagal reflex could thus be tested in any stage of asphyxia, rapidly or slowly produced, and the results obtained compared with those taken immediately prior to the attachment of the bag.

In order that the state of anæsthesia should be maintained at practically the same level throughout the experiment, a somewhat prolonged administration of vapour at a fixed percentage was given beforehand, so as to reduce the rate of absorption of chloroform before attaching the asphyxiating bag. The quantity of chloroform vapour contained in the bag was too small, even if largely absorbed, to influence the degree of narcosis to any considerable extent. There being, further, no tangible evidence of the destruction of chloroform in the body, there would not appear to be any probability of the production of a lessened anæsthesia during the process of asphyxia.

According to Morat and Doyon [13], Embley, and others, it is in the induction period of chloroform administration that the vagus centre manifests its greatest activity, both spontaneous and reflex. Unfortunately this stage of anæsthesia does not lend itself readily to experiments such as these, and therefore the condition of fully induced anæsthesia alone has been considered in this research.

Two series of experiments of this nature were performed, twelve under chloroform and eight under ether. The ether vapour was administered in a similar fashion to the chloroform and was controlled to a constant concentration, but the actual percentage value of it was not ascertained.

TABLE I.—EXPERIMENTS UNDER CHLOROFORM ASPHYXIA.

No.	1910	Percentage of chloroform	Stimulation: Strength	Stimulation: Duration	Reflex	Latent period of reflex
		Experiments in which the Reflex was Diminished only.				
1	July 19	1·5 per cent.	—	9 sec.	Progressive diminution and final suppression	Increased
2	,, 21	1·0 ,,	15 cm.	8 ,,	Marked diminution in final stages	Diminished
3	,, 22	0·5 ,,	Strong	10 ,,	Progressive diminution in latter half of tracing	Increased
4	,, 25	1·0 ,,	Strong	6 ,,	Early progressive diminution	,,
5	Aug. 19	0·8 ,,	20 cm.	5 ,,	Progressive diminution and final suppression	Unchanged
6	Sept. 9	1·5 ,,	6·5 cm.	7 ,,	Early and persistent diminution	Increased
7	,, 12	1·5 ,,	11 cm.	5 ,,	Early diminution and almost total suppression	,,
		Experiments in which the Reflex was Increased.				
8	Sept. 1	1·0 per cent.	6 cm.	—	Marked progressive increase diminution in final stage	Increased
9	,, 5	(*a*) 0·5 ,,	6 ,,	4 sec.	Marked progressive increase (asphyxia not carried to final stage)	Diminished
		(*b*) 2·0 ,,	6 ,,	2 ,,	Progressive increase in the first part diminution in final stage	,,
10	,, 15	1·5 ,,	Light	11 ,,	Marked increase ...	Unchanged
11	July 28	1·0 ,,		6 ,,	Slightly diminished at first, marked increase in middle stages. Asphyxia stopped when oxygen in bag reduced to 9·2 per cent.	Increased
12	Sept. 8	1·5 ,,	19 cm.	5 ,,	Slightly increased at first, diminution later	,,

An analysis of the above table shows that asphyxia under chloroform has a general tendency to cause diminution of the reflex under consideration. In the first seven of the experiments asphyxia caused diminution alone, most marked in the advanced stages, but sometimes quite evident in the earlier stages also (figs. 1 and 2). In every case (including the following five) in which the asphyxia was carried to completion some degree of diminution could be detected in the concluding stage—that is to say, at about the time of primary failure of

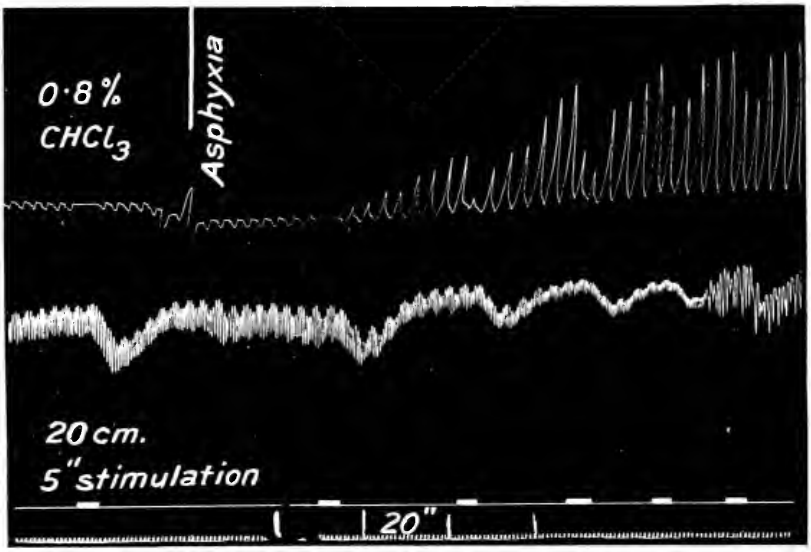

Fig. 1.

Asphyxia under chloroform, somewhat rapidly induced. Progressive diminution of the vagal reflex. The signal line also represents the blood-pressure zero. Time marked in seconds.

[*Note.*—All tracings to read from left to right. The upper tracing in each case represents the respirations. Where no abscissa line has been introduced the stimulation-signal line (in fig. 8 the time-line) serves to indicate the pressure zero.]

respiration. In the remaining five cases there was evidence of exaggeration of the reflex under asphyxia. Of these three showed increase only, except in the terminal phase, and the increase was progressive in two of them. In the last two cats both increased and decreased effects were observed antecedent to the terminal phase. Figs. 3 and 4 show well-marked instances of exaggeration of the reflex. The latent

period of the reflex is generally lengthened in asphyxia under chloroform independently of changes in the intensity of the reflex.[1]

As a control to the foregoing results I may briefly mention a series of experiments in which asphyxia was induced by causing the animal to inhale an irrespirable gas, either pure or diluted. The gases employed were hydrogen, nitrogen, and carbon dioxide, and chloroform vapour

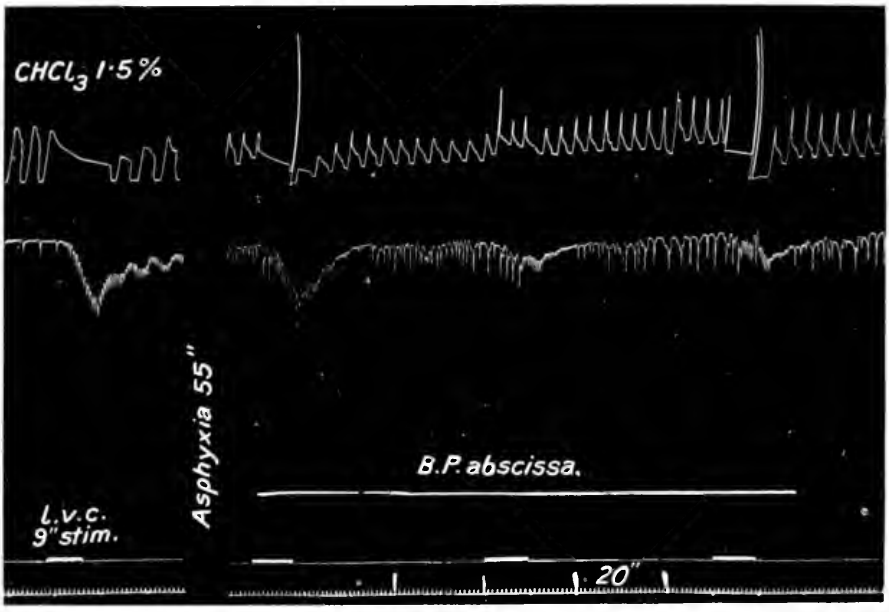

FIG. 2.

Asphyxia under chloroform. Progressive diminution of the vagal reflex. In the interval represented by the gap in the tracing, the asphyxiating bag was connected to the trachea tube, and the following vagal stimulation was made 55 seconds later. Time marked in seconds.

was given in the same proportion per atmosphere as was present in the previously inspired air. The administration was never conducted for a long period, and therefore no question of progressive anæsthesia could

[1] It is noteworthy that the simultaneous respiratory reflex undergoes a change in asphyxia under chloroform. Normally the arrest of respiration takes place in *inspiration*, but it gradually changes to well-marked *expiratory* arrest as asphyxia advances (fig. 3). This effect is not generally so well observed under ether anæsthesia.

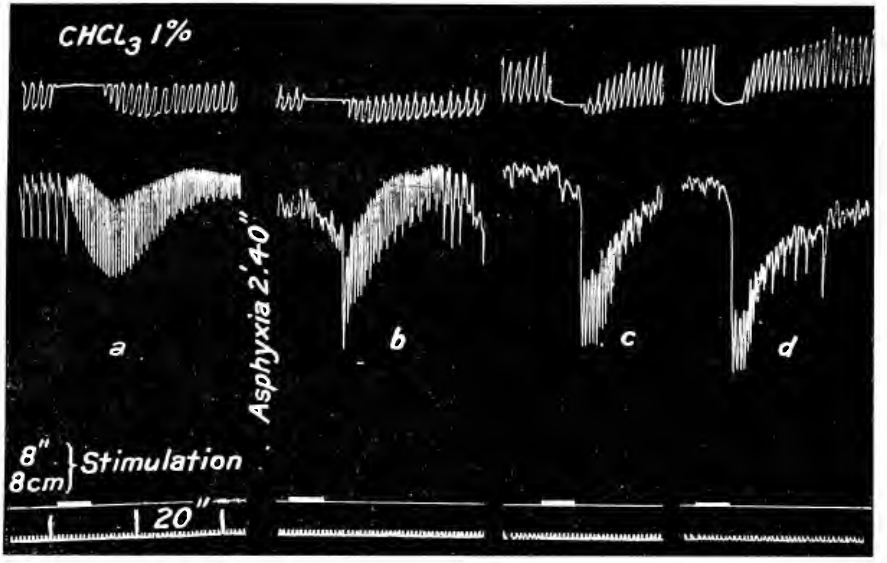

FIG. 3.

Asphyxia under chloroform, slowly induced. Progressive increase of the vagal reflex. The signal line also indicates the blood-pressure zero. *a*, normal reflex; *b*, 2 min. 42 sec. after commencing asphyxia; *c*, 5 min. 30 sec. after *b*. *d*, 2 min. after *c*. Time in seconds.

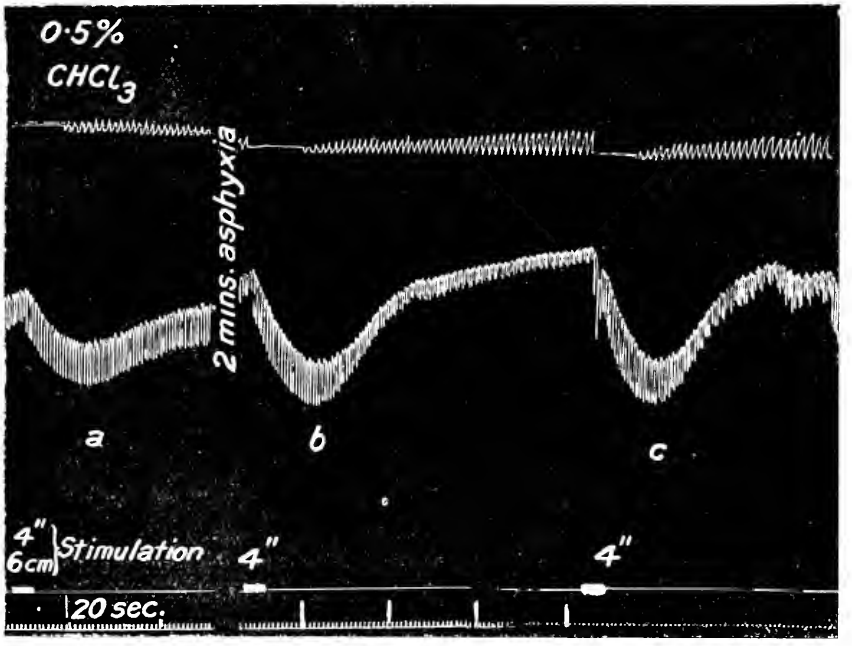

FIG. 4.

Asphyxia under chloroform. Progressive increase of vagal reflex. *a*, normal reflex *b*, 2 min. after bag connected; *c*, 1 min. 10 sec. after *b*. Time marked in seconds.

arise; further, artificial respiration being generally employed, variations in absorption, such as might be induced by the exaggerated respirations of asphyxia or by the reflex cessation of respiration during stimulation of the nerve were eradicated. These particular experiments were not uniformly satisfactory, but they served to substantiate, under the somewhat different conditions of asphyxia and anæsthetic administration,

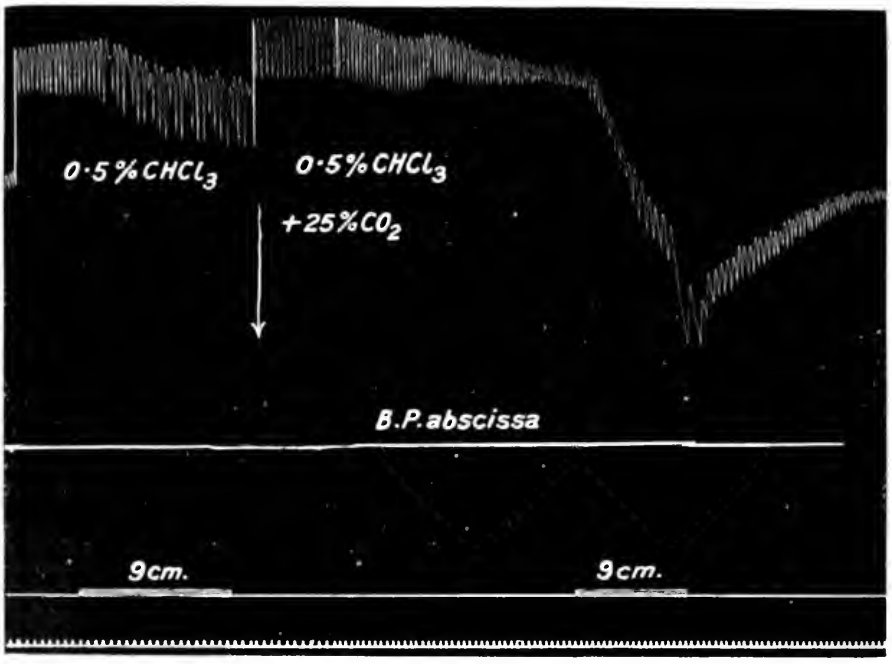

Fig. 5.

Increase of vagal reflex under 25 per cent. CO_2. Artificial respiration. Time marked in seconds.

the previously described observations that the vagus reflex is variably affected by asphyxial factors, but more commonly in the direction of decrease. In fig. 5 is shown a tracing of an exceptionally intense increase of the reflex under an atmosphere of CO_2 25 per cent., $CHCl_3$ 0·5 per cent., air 74·5 per cent. This particular experiment was repeated three times on the same animal, thus excluding the possible influence of fortuitous conditions.

There do not appear to be any diverse factors in the foregoing experiments to account for the irregular results, which are doubtless, therefore, due to interacting physiological processes. The respective parts played by the nerve-centres, the cardiac and general circulatory mechanism in modifying the inhibitory reflex during asphyxia, cannot be unravelled in the absence of further knowledge. It is, for instance, highly essential to ascertain the influence of asphyxia upon direct cardiac inhibitions caused by stimulation of the peripheral end of the cut vagus, but the difficulty of obtaining this reaction in the cat[1] has caused the postponement of further investigation.

Table II.—Experiments under Ether Asphyxia.

No.	1910	Stimulation		Reflex	Latent period of reflex
		Strength	Duration		
		Experiments in which the Reflex was Diminished.			
1	Sept. 19	9 cm.	7 sec.	Early total suppression	Unaltered
2	,, 21	6 ,,	4 ,,	Progressive diminution	Diminished
3	,, 30	5 ,,	4 ,,	Marked progressive diminution	,,
4	Oct. 4	10 ,,	4 ,,	Progressive diminution	Unaltered
		Experiments in which the Reflex was Increased.			
5	Sept. 28	6 cm.	5 sec.	Slight progressive increase	Unchanged
6	,, 28	6 ,,	5 ,,	,, ,,	,,
7	,, 29	5 ,,	4 ,,	Marked progressive increase	Diminished
8	Oct. 5	5 ,,	4 ,,	Slight progressive increase	,,

The ether asphyxia series is analysed in Table II. Here the instances of increase and decrease of the reflex are seen to occur in equal frequency, and in fig. 6 is shown a well-marked instance of the former variety. The latent period is more generally reduced in ether asphyxia, and there is not so marked a tendency towards total suppression in the final stage, otherwise the phenomena are very similar to those observed under chloroform asphyxia.

[1] *See* Hough, *Journ. Physiol.*, 1895. xviii, p. 163, in confirmation of this.

I may add that I have never observed any indication that a fatal result may be caused by a cardio-inhibitory reflex of any intensity, under either anæsthetic.

The conclusions arrived at from a consideration of this section are as follows:—

(1) Under chloroform the cardio-inhibitory reflex is obscured or suppressed by complete asphyxia.

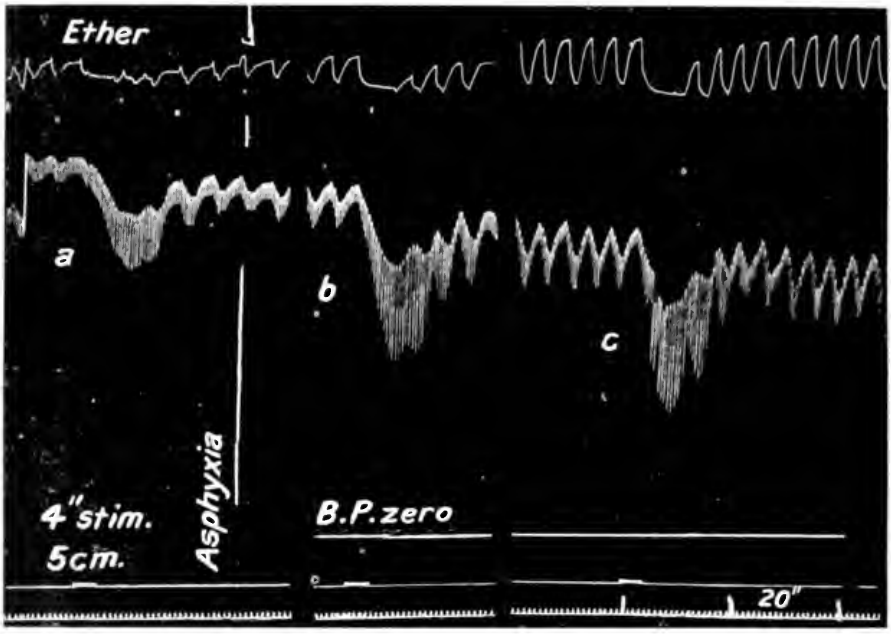

FIG. 6.

Asphyxia under ether. Progressive increase of the vagal reflex. The first gap represents an interval of 40 sec., the second gap an interval of 60 sec. Time marked in seconds.

(2) In a condition of partial asphyxia under chloroform the cardio-inhibitory reflex is variably affected, for it may be either diminished or increased in an apparently fortuitous manner, the intensified form of reaction being, on occasion, of a marked and significant character.

(3) Under ether, partial asphyxia also affects the cardio-inhibitory reflex in a similar diverse fashion, and the intensified reaction would appear to be no less frequent than under chloroform.

Section B.—Spontaneous Cardiac and Respiratory Failure in Asphyxia under Chloroform.

The form of asphyxia employed in the experiments considered in this section was, as before, non-obstructive, and hence all blood-pressure effects such as might be due to variations in intrathoracic pressure were avoided. The period of fully induced anæsthesia was alone studied, the stage of induction not being taken into consideration.

(*I*) *Cardiac Failure.*

Asphyxia under both chloroform and ether alike seldom causes more than a slight rise of blood-pressure, and frequently either no rise at all occurs or else an early decline may be found. The asphyxia manifests itself in a fall of pressure, which is generally late in onset and rapid in course, and appears to be conditioned simply by want of oxygen, as in asphyxia without anæsthetics. The slowing of the heart usually seen in the course of this fall is well ascertained to be due to concurrent asphyxial impulses from the cardio-inhibitory centre, and to be an accompaniment, and not a determining cause, of fall of pressure. In experiments under general anæsthesia the characteristic slow and regular vagal beats only occur when the asphyxia is practically complete, with a rapidly falling blood-pressure and failing respiration. Under ether this vagal beat is generally better marked than under chloroform.

Slowing of the heart-beat in asphyxia due to heart-block has recently been described by Lewis [10] and Mathison [11]. This appears from Mathison's paper to be late and irregular in onset in the intact animal, and, so far as I can judge from the data given, enters more into the consideration of those events following the stage in which asphyxia has become sufficiently acute to cause cessation of regular respiration.

Irregularities of the heart-beat, generally ascribed to vagal action on account of their non-occurrence when the vagi are cut (Hill and Flack [9], Mathison), are sometimes found in the presence of a partial deprivation of oxygen under chloroform, as in the stages of a gradually induced asphyxia prior to the respiratory and vascular climax (*see* fig. 7). Such irregularities are not infrequently observed, apart from asphyxia, in uncomplicated chloroform narcosis, but their onset does appear to be determined in some instances by partial asphyxia, and hence they must

be considered as asphyxial phenomena. The first part of this tracing shows irregularities which are in all probability due to vagal influence, but the second part, characterized by very rapid and small heart-beats, resembles the form which results when vagal action is cut out. In the course of this latter type of tracing, on rare occasions a sudden stoppage of the heart's action has been observed when the oxygen supply has

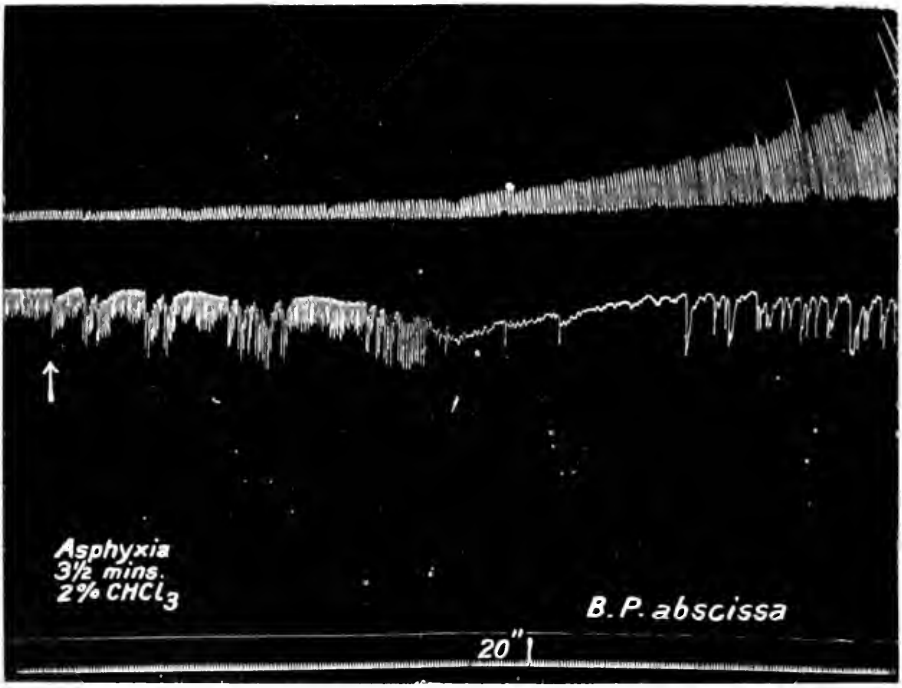

FIG. 7.

Forms of irregularity of the heart-beat in slow asphyxia under 2 per cent. chloroform. The asphyxiating bag was connected to the trachea tube 3 min. 30 sec. before the arrow mark. Respirations ceased very shortly after the terminal portions of the tracing shown. Time marked in seconds.

become very limited, giving rise to a not inconsiderable fall of blood-pressure. This fall is not permanent, but is subject to rapid recovery, complete or partial. The most pronounced instance of this kind which I have come across occurred in a cat which was being slowly asphyxiated under 0·8 per cent. chloroform; at the end of six minutes the pressure rapidly fell 58 mm. (from 146 mm. to 88 mm.), but soon recovered to

126 mm., the breathing ceasing in the final asphyxial stage two minutes later. It is impossible to define the cause of this form of irregularity from the blood-pressure tracings alone, but it is probable that it is not so much a sign of heart failure as an indication of vascular adjustment.

It does not appear, from the foregoing observations, that any serious permanent lowering of the mean blood-pressure follows from the irregularities of heart-beat which may be found in partial asphyxia, and these are probably therefore of little significance from a clinical point of view.

I have not met with any of the irregularities just described in the case of asphyxia under ether, the ether pressure tracing presenting a singularly even form up to the final stage. To anticipate later matter, it is in this freedom from irregularities alone that ether asphyxia compares with chloroform asphyxia to the disadvantage of the latter.

(II) The Arrest of Respiration.

The moment at which regular respiration ceased was adopted as an indication of the point when the oxygen in the blood became insufficient to support life and the asphyxial process might be considered complete. This primary arrest of regular respiration is a well-marked phase under anæsthetics (fig. 8); it follows very shortly after the asphyxial spasm, when this occurs, and is coterminous or nearly so with the asphyxial fall of pressure, although the heart does not actually cease beating until considerably later. The respiratory arrest is followed by a prolonged pause, which is succeeded in turn by a series of convulsive asphyxial gasps at long intervals. Two methods—(*a*) and (*b*)—were adopted for the investigation of this subject:—

(*a*) *Observations upon the Minimum Partial Pressure of Oxygen necessary to maintain Respiration.*—Cats were asphyxiated in the usual fashion by causing them to inhale an atmosphere containing either chloroform or ether vapour confined in a bag. The bag was withdrawn at the moment complete suppression of regular respiration supervened, and its contents analysed. The percentage of residual oxygen was taken as a measure of the animal's resistance to asphyxia under the respective anæsthetics. The time taken to induce complete asphyxia varied naturally with the extent to which the bag was inflated, which was not exactly ascertained, and therefore not taken into account in these experiments. Table III includes four experiments of this nature, the animals being tracheotomized but not subjected to any further operative procedure.

Table III. Prolonged Simple Asphyxia.

1910	Anæsthetic	Arrest of respiration in[1]	Analysis	
			O_2	CO_2
Oct. 7	Chloroform, 1·8 per cent.	13 min. 40 sec.	4·5 per cent.	11·3 per cent.
,, 10	,, 1·8 ,,	9 ,, 20 ,,	1·2 ,,	12·0 ,,
,, 7	Ether	10 ,, 10 ,,	1·6 ,,	8·3 ,,
,, 11	,,	6 ,, 20 ,,	5·5 ,,	9·4 ,,

[1] The time taken to arrest respiration was dependent on the extent of inflation of the bag, which was not controlled.

The two results obtained under chloroform, and the first of the two under ether, agree with the observation of Paul Bert [1] that the lowest respirable percentage of oxygen for the cat, when not under the influence of an anæsthetic, is an average of 4·4 per cent. In the second ether case the respiration failed at a somewhat higher percentage (5·5 per cent.). It is, therefore, apparent that the respiratory centre is neither more nor less resistant to uncomplicated asphyxia under chloroform than in its absence. Under ether, asphyxia would appear from the above results to be somewhat more lethal in its effects.

It is interesting to note that a greater excretion of CO_2 occurs under chloroform asphyxia than under ether asphyxia. This is a constant phenomenon, and there is a good deal of collateral evidence regarding the increased production and output of CO_2 under chloroform (Buckmaster and Gardner [6], Collingwood [2], Glasgow Committee [14]). This is not, however, a matter for present discussion, inasmuch as the highest of these percentages is non-lethal, and consequently the differences noted can have no significance in relation to the subject under consideration.

In addition to the above, other analyses were made of the contents of the bag in the case of some of the experiments described under Section A, and the results must be considered separately, for the conditions represent more closely those of a subject undergoing manipulations in the course of a severe operation. As previously described, the animal was tracheotomized, a cannula inserted in a carotid artery, one vagus divided and its central end stimulated at intervals. The analysis was made, as before, as soon as respiration ceased.

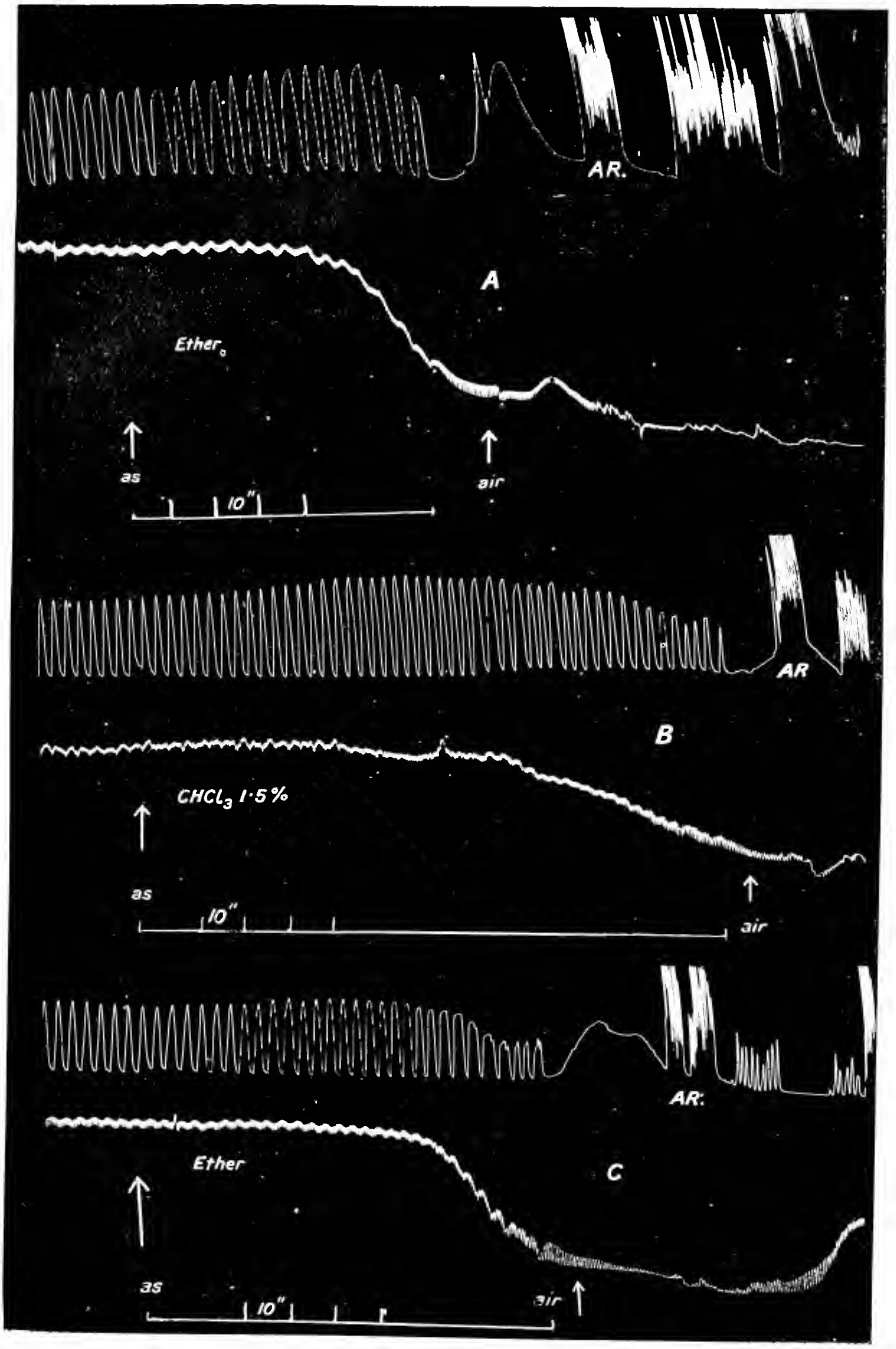

FIG. 8.

Asphyxia under chloroform compared with asphyxia under ether in the same animal. A and C are tracings of asphyxia under ether. B is a tracing of asphyxia under chloroform. The horizontal lines, bearing time markings in periods of 10 sec., represent the blood-pressure zero and also, by their length, the duration of the asphyxia up to the moment of the cessation of regular respiration. A R = artificial respiration. Respirations recorded from abdomen.

TABLE IV.—PROLONGED COMPLICATED ASPHYXIA.

1910	Anæsthetic	Arrest of respiration in [1]	Analysis	
			O_2	CO_2
Oct. 12	Chloroform, 2·0 per cent.	8 min. 40 sec.	4·5 per cent.	10·0 per cent.
Aug. 19	,, 0·8 ,,	6 ,, 40 ,,	4·0 ,,	10·4 ,,
Sept. 21	Ether	7 ,, 0 ,,	5·3 ,,	8·5 ,,
,, 28	,,	4 ,, 30 ,,	6·6 ,,	7·6 ,,
,, 29	,,	6 ,, 50 ,,	7·0 ,,	8·8 ,,
,, 30	,,	3 ,, 10 ,,	6·6 ,,	7·0 ,,
Oct. 5	,,	3 ,, 30 ,,	6·5 ,,	6·4 ,,

[1] See footnote to Table III.

The two chloroform records in the above table show an oxygen percentage remaining in the bag which is very much the same as was found under uncomplicated asphyxial conditions (Table III). The average of the oxygen percentages in the experiments under ether is notably raised, being 6·4 per cent., as against 5·0 per cent. shown in Table III. The amount of CO_2 found under both anæsthetics averages somewhat less than in simple asphyxia. The average CO_2 under ether is again found to be less than that under chloroform, but it is possible that, in this series, the notably larger remnant of O_2 in the ether cases may be partially responsible for the difference.

The foregoing figures demonstrate that a smaller quantity of oxygen will generally maintain respiration under chloroform in the presence of severe operative measures than will suffice under ether with similar conditions, and that therefore asphyxia under ether may prove more detrimental than chloroform asphyxia.

(b) Observations on the Time Incidence of Cessation of Respiration.—The factor of time incidence was investigated by attaching to the trachea a thin rubber bag of about 20-c.c. capacity—i.e., just large enough to allow free respiratory movements to take place. The animal being put under one of the two anæsthetics under consideration, the bag, fully inflated with air only, was attached and left on until the respiration failed; it was then restored by artificial respiration and re-subjected to asphyxia in the same way under the other anæsthetic. There is no positive standard of depth of anæsthesia, but this was adjusted so as to be equal, as far as could be judged, under the two anæsthetics, and corresponding to that of ordinary surgical anæsthesia.

TABLE V.

Number of experiment	Anæsthetic	Initial blood-pressure	Breathing ceases in	Remarks
No. 1	(1) Ether	128 mm.	2 min. 12 sec.	Restored by artificial respiration
	(2) Chloroform, 0·5 per cent.	76 ,,	2 ,, 12 ,,	,, ,,
No. 2	(1) ,, 1·0 ,,	132 ,,	2 ,, 5 ,,	,, ,,
	(2) Ether	126 ,,	1 ,, 38 ,,	Failed to restore animal
No. 3 (fig. 8)	(1) ,, ...	126 ,,	1 ,, 8 ,,	Restored by artificial respiration
	(2) Chloroform, 1·5 per cent.	86 ,,	2 ,, 14 ,,	,, ,,
	(3) Ether	90 ,,	1 ,, 32 ,,	,, ,,

The numbers in parentheses indicate the order in which the anæsthetics were administered.

It is evident, from the three experiments in the table, that the respiratory centre may be affected more rapidly by asphyxia under ether than under chloroform, for in two of them the ether asphyxia is a more acute process than is the chloroform asphyxia, and it is further noticeable that, whereas all the animals were restored by artificial respiration after chloroform, one of them could not be restored by these means after ether. Asphyxia is, therefore, certainly not in this respect a more serious complication under chloroform than it is under ether, when it has the clinical reputation of being comparatively harmless.

A final word may be added in relation to the incidence of fatal suffocation arising from an accidental complete occlusion of the air-passages during anæsthesia. It is stated by Richet [16] that chloroformed animals support asphyxia as well as, if not better than, animals which have not been anæsthetized, and that it is always possible to restore them for some minutes after the cessation of respiration. This observation does not accord with my own experience, for I have met with cases, both under chloroform and under ether (but more frequently under the latter), in which I failed to restore the heart-beat. This subject is, I think, worthy of investigation, for some of the asphyxial symptoms are not strongly evinced under chloroform, and so there must exist a suspicion that the nature of a suffocative process may not be properly recognized. The following considerations have to be borne in mind in connexion with this matter :—

(1) In complete obstructive asphyxia there is a greater privation of air than in the case of any of the non-obstructive experiments described

in the foregoing part of this paper, and hence the cessation of respiration comes about within a shorter period.

(2) Asphyxial spasm is practically suppressed at any higher concentration of chloroform than 1 per cent., and indeed this important sign may be altogether lacking. I have never found it entirely wanting under ether.

(3) The respiratory movements may be restrained by the obstruction, when full anæsthesia is maintained, from showing their asphyxial exaggeration.

(4) The mechanical influence of the asphyxial respirations may induce an earlier fall of blood-pressure than in the non-obstructive form of asphyxia.

These remarks are, of course, merely suggestive, and do not lead to any positive conclusion in respect of the possibility of death from suffocation under chloroform in ordinary clinical conditions.

General Conclusions.

So far as the scope of these experiments extends, they do not afford any evidence to justify the assumption that asphyxia, whether partial or complete, is a more serious complication in any important respect under chloroform than under ether narcosis. In both cases asphyxia is evidently undesirable, and of the two there is evidence that asphyxia under ether is the more active in affecting the respiratory centre.

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THE DEVELOPMENT OF THE CORTEX IN THE HUMAN SUPRARENAL GLAND AND ITS CONDITION IN HEMICEPHALY.[1]

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From the Medical School of University College Hospital.

(Plates LIV. and LV.)

It has long been remarked that the human suprarenal gland at birth, and for some months before birth, is surprisingly large in relation to the bulk of the kidney; but the history of this peculiar enlargement and its nature, as to whether it consists of medulla equally with the cortex, has not been made altogether clear. We were confronted with this question when attempting to analyse the alterations that occur in the suprarenal cortex during various diseases, as the suprarenals of children in the first year of life were found to present certain appearances that at the outset seemed pathological, but were soon recognised as being evidence of a natural phase in the development of the gland. This change is a very obvious one, but, so far as we have been able to ascertain,[2] it has not been described hitherto, and a brief anatomical account of it, therefore, becomes necessary to clear the ground for a later description of the true pathological changes.

Broadly, the main fact is this, that the abnormal size of the human suprarenal is caused by a peculiar hypertrophy of the cortex in fœtal life, while at once after birth this hypertrophied tissue degenerates rapidly and its place is taken by the slow growth of cortical cells in the periphery of the gland. At birth the gland is composed of the narrow rim of cells from which comes the adult cortex, of an enormous mass of fœtal cortex which will immediately degenerate, and of a thin core of medulla. The first and the last steadily enlarge, the middle mass atrophies; and therefore at the third postnatal month the absolute weight of the gland is less than at birth. At the end of the

[1] Received January 31, 1911.

[2] Since this paper was written our attention has been called to preparations made by Dr. Kohn in Professor Aschoff's laboratory at Freiburg, which also illustrate a series of events here described.

first year the degenerated cortex of fœtal life has vanished, and the gland assumes the normal appearance of adult life, though in miniature, for it has still much growth before it.

Methods.

The glands were removed from the body as soon as possible after death, at times varying from two to twenty-four hours, and hardened for a couple of days in a mixture of equal parts of 10 per cent. formalin and Müller's solution. The sections were cut in gum on a freezing microtome, and stained for fat by scharlach R, with Weigert's hæmatoxylin as a counterstain. Mounted in pure glycerin, they kept their colour permanently. The chromate salts of the Müller's solution and the scharlach R indicate the chief substances of medulla and cortex (1906 [1]) respectively, so enabling either tissue to be recognised.

The *cortex*, normally, is loaded in man with a fatty substance. This cortical "lipoid" is peculiar in that it is doubly refractive when stored in its highest form in the resting gland. It may be lodged in any area of the adult cortex, and we therefore do not recognise the usual division of the latter into three zones. The fatty substance disappears rapidly in various pathological conditions that are associated with fever, when the gland may be exhausted also of its chromaffine stain and adrenalin. But even in its absence the cortical cells are generally easy of recognition.

The *medulla* never contains fat in its own cells, though cortical cells are often intermingled with them, and so lend an appearance of the presence of fat. By its chromaffine stain, Kohn and other workers have proved the identity of the medulla with similar adrenalin-yielding cells that are scattered over the body in relationship to the sympathetic ganglion cells, and Kohn (1903 [2]) speaks of them as paraganglia. At birth the main mass of chromaffine cells is outside the suprarenal and along the ventral surface of the abdominal aorta. These outside paraganglia slowly dwindle in size, while the medulla of the suprarenal grows, but there is not the great development of a fœtal mass with its immediate postnatal degeneration that characterises the history of the cortex. Still the life-history of the chromaffine cells does resemble, in some degree, that of the cortex; so that, generalising roughly, one may say that the fœtal cortex, which was so large, and the fœtal paraganglia perish and are replaced by a new cortex and a new medulla which constitute the adult gland.

So far as we have seen, though the question was not examined closely, there is no indication of a similar change in the development of the suprarenal glands in other mammals. Thus the gland of the guinea-pig, which in adult life acquires a relatively huge mass of cortical cells, at birth is quite minute. The apes we have not had the opportunity to study.

A description of sections of the human gland at successive epochs of life will make the point clear. The sections reproduced were drawn

by hand carefully on the same scale of projection, and indicate with fair accuracy the relative width of the cortex at each stage; but they do not give a complete picture of the development of the medulla. The thickness of the cortex is much the same all over the gland: the medulla varies greatly, and it is always aggregated in a big mass close to the exit of the main central vein. Consequently, to determine the true relation in bulk of cortex and medulla, it would be necessary to sum the entire areas of serial sections of the whole gland, as was done previously in the study of various animals.[1] Such accuracy was not needed for our purpose; and we therefore were content to measure the depth of the cortex in a transverse section taken across one of the triradiate leaves at some place where a little medulla was seen to be present. Any of the glands would at some section have shown a very much larger central mass of medulla than is represented in the drawings. The sections were cut transversely to the central vein and in a plane perpendicular to the surface of the gland, so that the cortical columns are given in longitudinal section, and not exaggerated by obliquity.

Observations on Normal Specimens.

Fœtus, 3·3 cms. in length, that is early in the third month. The mass of cortical cells is closely associated with the kidney and about equal to it in size, while the smaller "sympathoblasts" lie in a separate clump outside. This distribution is well illustrated in the diagram of Kohn, which Poll (1906 [2]) has reproduced in his monograph. The cells in the interior of the cortical mass are enveloped in wide vascular spaces, and have much larger cell-bodies than those at the periphery.

Fœtus, 7·5 cms. in length, at the end of the third month (Plate LIV. Fig. 1). The cortical cells are large and well developed, except at the outer rim, and contain some of the fatty substance. The latter, however, is not shown in the drawing. Scattered here and there are islets of small, darkly-stained cells like lymphocytes, that a little later will enlarge and take the chromaffine stain. The periphery of the mass is occupied by a narrow rim of small, closely aggregated, cortical cells.

Fœtus of seventh month (Plate LIV. Fig. 2). The chromaffine cells are still in scattered islets, but they now take a brilliant yellow stain, which is not represented in the drawing. The cortex has developed rapidly and stains lightly all over with scharlach, but the lipoid substance is lodged mainly in the outer rim.

Fœtus at full term. — All the specimens of these were from cases of placenta prævia, or some similar condition which led to the child's death by asphyxia. Consequently the glands were greatly congested and somewhat distorted. The inner cortical cells constitute a mass about four times as deep as the outer: they are separated by widely dilated capillaries and seem quite healthy. The fatty substance is lodged only in the outer rim of smaller cells, but the columns of these pass without any clear line of demarcation into continuity with

[1] Elliott and Tuckett, *loc. cit.*, p. 338.

the inner mass. The medulla is now entirely central, the outlying islets having vanished.

Child, *æt.* 12 *days*, normal birth, and death by broncho-pneumonia after three days' illness (Plate LIV. Fig. 3).—The change in the cortex, which can be seen three or four days after birth, is now strikingly evident. The outer rim (A) has deepened a little, and its cells are well stained, healthy, and loaded with lipoid. They are sharply demarcated from the rest of the fœtal cortex; the cells of the latter in the wide inner zone (B) are swollen, stain ill, and many of them are laden with droplets of fat that seem to be the outcome of ordinary fatty degeneration, for they do not disappear like the true cortical fat in phases of exhaustion of the gland. Such areas of fatty change are not universally distributed. The drawing is from a particularly rich area. But the contrast between the persistent and the dying cortex is very marked in every section that was examined. Whether the fat be a degenerative product, or akin to that secreted by the healthy suprarenal cortex, is uncertain; the question does not affect the main fact of the degeneration of the inner zone. No obvious changes in the cortical blood vessels could be detected as a cause of this degeneration. The medulla is represented by clusters of the usual cells close to the central vein.

Child, *æt.* 11 *weeks*, died of general wasting (Plate LV. Fig. 4). The illness had deprived the cortex of much of its lipoid substance. The cells of the fœtal cortex (B) have almost disappeared, except for a few showing traces of fat close to the central medulla: the vessels between them are congested. Under a higher magnification it could be seen that the cell columns of the active growing cortex pass continuously into those of the fœtal cortex, which are shrunken and degenerate.

Child, *æt.* 5 *months*, died of miliary tuberculosis, with three weeks' illness (Plate LV. Fig. 5). One gland weighed 1·5 grm., that is a little less than the normal weight at birth. The cortex (A) is laden with fat and doubly refractive crystals. Between it and the medulla is a very narrow strip of vascularised strands of connective tissue, containing here and there a degenerating fatty cell (B).

This instance is of an unusually rapid disappearance of the fœtal cortex. Traces of the latter generally persist as a band of vascularised connective tissue until the eleventh or twelfth month. After the first year we have in no case seen any vestige left, except it be in the so-called fibrous septum between cortex and medulla.

The changes illustrated in the microscopic sections are suggested also by the alterations in bulk of the gland. At birth it is massive: in three or four months it is shrunken to a triradiate form, and the external surface of the cortex is wrinkled and folded. Despite subsequent growth of cortex and medulla up to adult life, the gland never again assumes the massive appearance that it had at birth.

The subjoined table gives the actual depth of cortical rim (A) and fœtal cortex (B) in hardened sections from various specimens. All these, of course, were from bodies that had suffered from some pathological process, so that the series is only of value in showing the main trend of the changes: the individual measurements are not of great consequence. In most cases the weight of the glands, unfortunately,

could not be taken, because to do so would have involved considerable delay under the conditions when the specimens were obtained.

In the fatty tissue around the capsule of the gland small isolated masses of cortical tissue are always present in the fœtus; and, while the majority of these atrophy, some persist to later life and present the same appearance as the adult cortex, containing abundance of lipoid.

Age.	Cortical Rim (A).	Fœtal Cortex (B).	Weight of One Gland.
Fœtal—			
3rd month (7·5 cms. long)	0·18 mm.	0·90 mm.	
7th month	0·23 ,,	0·75 ,,	
Full term	0·34 ,,	1·12 ,,	2·2 grms.
Anencephalic, full term	0·42 ,,	0·0 ,,	0·32 ,,
Exophthalmic goitre, full term	0·38 ,,	1·12 ,,	2·3 ,,
Postnatal—			
12 days	0·47 ,,	0·76 ,,	1·8 ,,
5 weeks	0·57 ,,	0·57 ,,	
8 ,,	0·66 ,,	0·19 ,,	
12 ,,	0·76 ,,	0·19 ,,	
21 ,,	0·6 ,,	0·09 ,,	1·5 ,,
36 ,,	0·76 ,,	0·04 ,,	
1 year	0·66 ,,	0·0 ,,	
2 years	0·76 ,,	0·0 ,,	
Adult	0·95 ,,	0·0 ,,	4·5 ,,

Observations on an Anencephalic Fœtus.

It is an old observation, dating back to Morgagni (1723 [4]), that in cases where, at birth, the cerebral hemispheres have failed to develop, there the suprarenal glands are abnormally small, though never absent. In a careful review of previous work on this question, Zander (1890 [5]) showed that in these cases of so-called "hemicephaly" the ganglia of the sympathetic nervous system are fully developed; and, further, that such aplasia of the suprarenals is never associated with spina bifida or hydrocephalus. It accompanies only the one condition, that of absence of the cerebral hemispheres and mid-brain.[1]

Naturally, in these earlier papers, the development of the chromaffine tissue in the paraganglia outside the suprarenals was not considered; and without such knowledge there is no support for Ilberg's [6] suggestion that the failure of the brain to develop follows as a consequence of a low blood pressure due to aplasia of the suprarenal glands.

With regard to the suprarenal itself most writers state that the

[1] Lovet and Nicholls, *Brit. Med. Journ.*, London, 1906, vol. ii. p. 919, describe a case of osteogenesis imperfecta with "small adrenals." Unfortunately no measurements are recorded by these authors to indicate the actual size of the glands. In a very typical case of a full-grown child with numerous fractures, that lived to the sixth day, we found the glands to be quite normal, weighing each 2·7 grms.

aplasia concerns medulla and cortex equally.[1] With this our observations, which, however, were made on but one specimen, are at variance. The case was that of a full-term child in which the cerebral hemispheres, the corpora quadrigemina, and the cerebellum were missing. The child lived for three days, maintaining normal temperature and blood pressure, while it exhibited lively nervous reflexes as far up as the level of the fifth cranial nerve. At the autopsy the suprarenals were in their usual position, but were small, weighing about one-sixth of the normal at birth (aggregate 0·65 grm.); their shape was trifoliate and flattened, precisely like a miniature of the suprarenal of a child one year old.

The paraganglia down the front of the aorta were stained with Müller's solution and found to be normally developed and loaded with chromaffine substance. The sympathetic ganglia were all normal. Sections of the suprarenal (Plate LV. Fig. 6) made it clear that the medulla was of normal size, or even a little larger than usual: so too was the external rim (A) of fat-holding cortex. Between the two was practically nothing to represent the mass of the "fœtal" cortex. This fœtal development had failed. Otherwise the tissues of the gland were in every respect normal, so that in section as well as in general appearance the gland was indeed a miniature of that of an infant one year old in which all vestige of the fœtal cortex is gone.

An attempt was made to confirm this analysis of the nature of the suprarenal defect by examining the glands in several Museum spirit specimens; but this was fruitless, inasmuch as they were found to be in too poor condition for histological study.

Summary.

The large size of the *human* suprarenal gland during fœtal life is due to a peculiar hypertrophy of the cortex, which commences very early and continues until birth. This inner hypertrophied mass is richly supplied with blood vessels, but it does not store in its cells the characteristic doubly refracting fatty substance which is a chief secretion product of the cortex.

Immediately after birth the inner mass of hypertrophied cells degenerates, undergoing fatty change; and at the end of the first year all trace of it has disappeared. Hæmorrhages occur readily in this degeneration zone, which, in consequence, has been wrongly depicted in some text-books as medulla damaged by hæmorrhage.

Enveloping the mass is a rim of smaller cells that early in fœtal life assume the appearance of the cells of the adult cortex and store up fatty substance. These develop steadily and, alone, form the adult cortex.

[1] Wiesel states that the chromaffine system especially is at fault, and that the zona reticularis is lacking from a cortex which is normal in respect of its glomerulosa. "Die Erkrankungen der Nebennieren.," Neusser und Wiesel, Wien, 1910, S. 78.

In a case of "hemicephaly," a child born without cerebral hemispheres, the characteristic small size of the suprarenals was due to the absence of the "fœtal" cortex: the rim corresponding to the adult cortex was almost normal, so too was the system of chromaffine cells. The suprarenal of the brainless child develops, therefore, in the same manner as does that of the animals.

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3. Poll . . . . . "Hertwig's Handbuch der Entwickelungslehre der Wirbelthiere," 1906, Bd. iii. Erster Teil, S. 442.
4. Morgagni . . . . . "Epistol. Anat. xx. a." The reference is given by J. F. Meckel; "Handbuch der path. Anat.," 1812, Bd. i. S. 642.
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6. Ilberg . . . . . *Arch. f. Psychiat.*, Berlin, 1901, Bd. xxxiv. S. 140.

DESCRIPTION OF PLATES LIV. and LV.

Sections of human suprarenal glands at successive dates of fœtal and postnatal life; drawn to same scale. Fat coloured red: doubly refractive crystals are not indicated. Medullary cells are stained dark blue by the hæmatoxylin, the chromaffine yellow not being shown. Blood in congested capillaries (Figs. 4 and 6) is stained a greenish yellow by the chromate salts.

The subjoined lettering applies to all the figures:—

A. Outer rim of cortex.
B. Enlarged cells of fœtal cortex.
C. Islets of medullary cells.

Plate LIV.

Fig. 1.—*Fœtus, 7·5 cms. in length,* at end of third month.

Fig. 2.—*Fœtus, 7th month.*—A is loaded with anisotropic fat. B is scattered irregularly in the gland, and a dark blue clump of it is seen at the very periphery of the cortex between the red cortical cell columns.

Fig. 3.—*Child,* 12 *days old.*—C abuts upon the central vein, and the corresponding other half of the section is not shown. The fat in B is probably a degeneration product.

Plate LV.

Fig. 4.—*Child,* 11 *weeks old.* Illness had somewhat exhausted A of fat. The vessels in B are, as so frequently, congested, but there has been no actual hæmorrhage.

FIG. 5.—*Child, 5 months old.*—A is loaded with doubly refractive lipoid. In the shrunken zone of B a few fatty cells still occur.

FIG. 6.—*Brainless child at full term,* "hemicephalic monster."—B is practically non-existent. Between the distended blood vessels pass columns of fat holding cells that belong to A.

This has been drawn on a slightly larger scale to give more detail. Consequently the depth of the cortex must not be compared directly with the depths in Figs. 1 to 5. The relative depth is given in the table on p. 485.

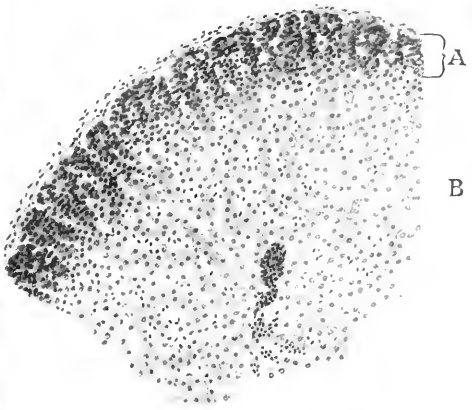

FIG. 1.

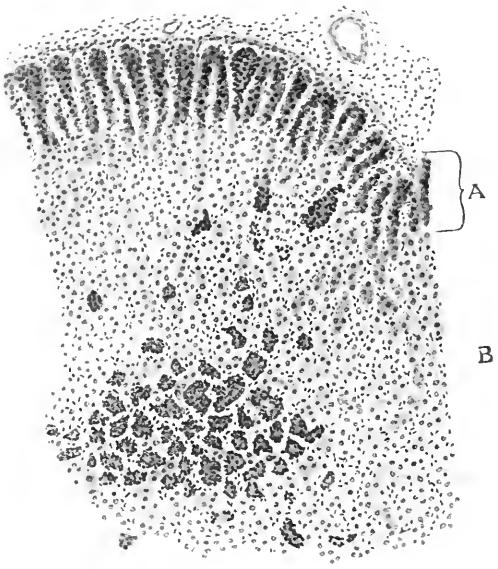

FIG. 2.

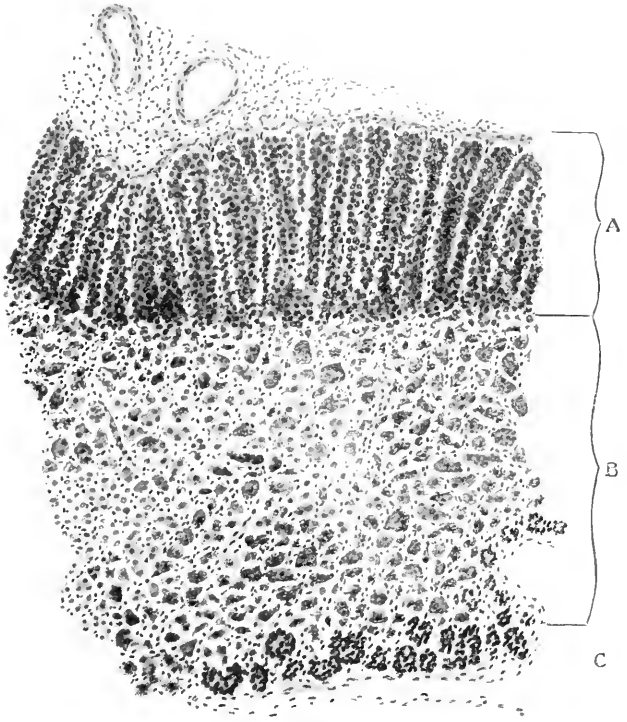

FIG. 3.

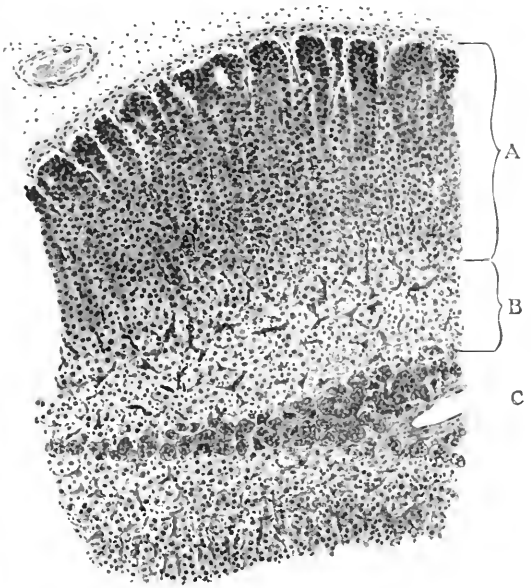

FIG. 4.

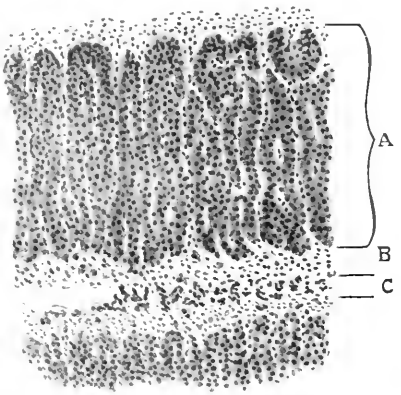

FIG. 5.

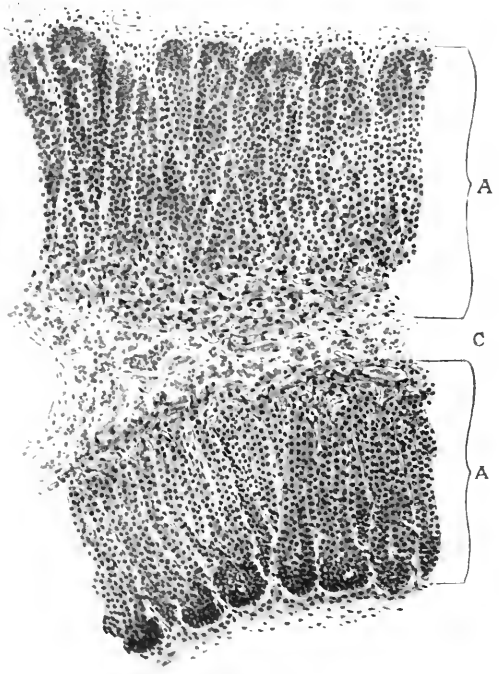

FIG. 6.

[*Reprinted from the* Proceedings of the Royal Society of Medicine, *April*, 1911.]

The Electrocardiographic Method and its Relationship to Clinical Medicine.

By Thomas Lewis, M.D.[1]

A Brief Description of the Galvanometer Method.

Galvanometers, instruments constructed to measure electric current, and electrometers, instruments constructed to measure electric potential, have been in general use in the physiological laboratory for many years. The time at my disposal will not permit me to detail the history of our knowledge of these instruments. It will be convenient if I turn immediately to the latest development, the introduction of the new "string galvanometer" of Einthoven. It is an instrument which, on account of the quickness of its response, its sensitivity and the ease with which it is managed, is rapidly superseding all other instruments of its class. It consists of a powerful electromagnet, the separate poles of which are closely approximated, and leave between them a narrow chink (fig. 1). In this chink an extremely fine fibre (of platinum or silvered quartz) is suspended. The principle of the instrument is simple. When you pass an electric current through a conductor lying in a magnetic field, conductor and magnet react upon each other, and if one system is fixed and the other is movable, the latter (the movable system) is deviated in a definite direction. In the string galvanometer the magnet is fixed, the string is slack and flexible; the string is the movable

[1] Working under the tenure of a Beit Memorial Research Fellowship.

system, and it deviates when a current is passed through it. The quickness and sensitivity of the instrument depend upon the lightness of the fibre and upon the strength of the magnetic field. The strength of the magnetic field of the string galvanometer and the lightness of the fibres are such that accurate measurements may be made of very minute currents. When the instrument is properly adjusted the deviation of the string is directly proportionate to the strength of current passed through it.

I shall pass over the history of our knowledge of the electric changes which accompany the contraction of muscle and the heart-beat,

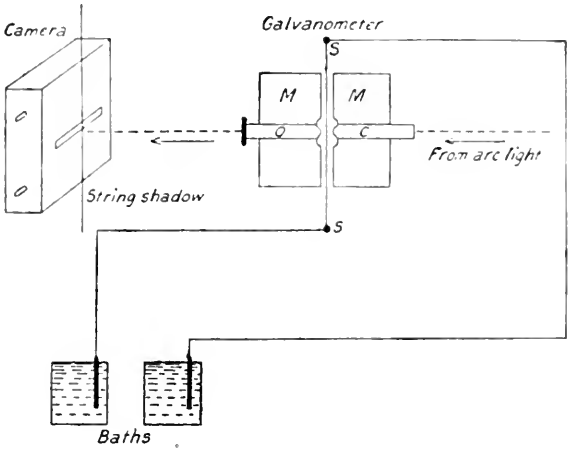

FIG. 1.

A simple scheme showing the arrangement of the apparatus used in securing electrocardiographic curves. It consists essentially of the galvanometer, arc light and camera. The galvanometer consists of a powerful electromagnet, *M M*, between the poles of which is a slit in which lies a string, *S S*, of extreme tenuity and composed of platinum or silvered quartz. The string is connected to a circuit which is completed by the patient, whose limbs are immersed in the baths. The beam of light from the arc light falls through the condenser, *C*, and the shadow of the moving string is projected by means of the microscope, *O*, on to the camera. The shadow of the string lies vertically, the slit of the camera lies horizontally, and the movements of the shadow are at right angles to it. Photographic paper is unwound by means of a mechanical arrangement behind the slit.

and turn to the more important facts now known to us, and which immediately concern us.

When a contraction is started in a muscle strip, be it somatic or cardiac, the point at which activity first manifests itself becomes

relatively negative to all other points of the strip surface. The activated or contracting end stands in electrical relationship to the inactive end of the strip, as does the zinc terminal of a Daniel cell to the copper terminal. If the ends of the strip are connected to a sufficiently sensitive galvanometer the electric change in the muscle is recorded by a deviation in a given and known direction. Now when a strip of muscle contracts the state of contraction or activity travels from one end of it to the other; at first the proximal or stimulated end is active, and consequently relatively negative to the distal end. Later, as the contraction wave passes to the distal end and the proximal

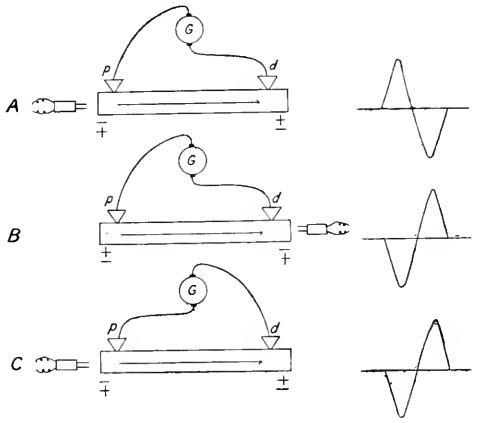

FIG. 2.

A diagram illustrating certain principles of electrocardiographic work. In *A*, *B* and *C* straight strips of muscle are diagrammatized, from the ends of which leads are taken with non-polarizable electrodes to the galvanometer, *G*. In *A* the muscle is stimulated to the proximal end, *p*, and the contraction travels from *p* to *d*. While the contraction is at *p*, *p* is negative to *d*. When the contraction reaches *d* and subsides at *p*, *d* becomes negative to *p*. A diagrammatic representation of the curve obtained is shown to the right of the figure. In *B* the muscle is stimulated at the distal end, and the events are reversed. The contraction passes from *d* to *p*, *d* is first negative to *p*, and later positive to *p*. The type of curve shown to the right is the reverse of that given in A. In *C* the stimulation and direction of the contraction wave are the same as in A, but the electrodes are reversed; *p* is first negative to *d*, and later positive. The type of curve is the same as that yielded by *B*.

end becomes quiescent the electric condition is reversed, and the galvanometer shows a deviation which is contrary in direction to the original deviation. The complete electric effect is termed a diphasic effect. Now the actual shape of the curve need not delay us, but it is important for

us to note that it is dependent upon two factors: first, the point at which the contraction wave starts, and secondly the relationship (in space) of the muscle mass (and all its parts) to the leading off electrodes. Stimulate the muscle at the opposite end and reverse the series of events of the contraction wave, and you obtain a complete and exact reversal of the electric effects. Maintain the point of stimulation and reverse the electrodes, you obtain a similar result. These two facts illustrate the essential principles which must be constantly borne in mind in dealing with the electrocardiogram (fig. 2).

What is the electrocardiogram, and how is it secured? An electrocardiogram is a photographic representation of the electric changes occurring between any two points of the body surface as a result of the heart-beat. It may be obtained by means of special electrodes applied to the base and apex of a heart under experimental conditions. The lead from base and apex of the heart is used because it represents, approximately, the general direction in which the muscle contracts; any other lead will yield an electrocardiogram, but it is essential to fix upon one or more definite leads for the sake of uniformity and comparison, and base-apex leads are usually employed. The electric changes at base and apex of the heart are not confined to them, they spread into the surrounding tissues in contact with them. In human galvanometric work the instrument is usually connected to what closely corresponds to a base-apex lead; a lead from the right arm and left leg is utilized, a lead equivalent to one from the right shoulder and left groin. Others are adopted, but I intend to confine attention to this single lead for the time being.

It is sufficient to connect the right arm and left leg of a patient by means of suitable electrodes, for example, baths of salt water (fig. 1), to the ends of the string (S S) of the galvanometer, to set this string in motion. The movements are minute, but may be magnified and projected by means of a microscope (O C) driven through the poles of the magnet (M M) on to a convenient photographic screen (fig. 1). A beam of light, falling through a condenser upon the string, projects the shadow through the objective. The shadow lies vertically, and at right angles to a slit, behind which a sensitive film is moved on rollers. The shadow moves from side to side across the slit, and hiding the sensitive paper from the light, leaves the impress of its movements upon it.

Up to the present I have described to you the working principles of the instrument, and you have the general idea of the manner in which

records are obtained. I have also spoken briefly of the electric changes which accompany contraction in muscle, and have drawn your attention to two important considerations. The curve which is obtained from a contracting muscle depends upon the lie of the muscle in relationship to the leading off electrodes. We need not consider this factor further, for I propose to speak of the single lead—that from the right arm and left leg. Of far greater importance to us at present is the fact that the shape of curve depends upon the direction taken by the wave of contraction in the heart muscle itself.

We may proceed to consider the form of the physiological electrocardiogram, and I shall pass from this to a description of a number of selected electrocardiographic curves of pathological form. The instances given must be regarded only as illustrative.

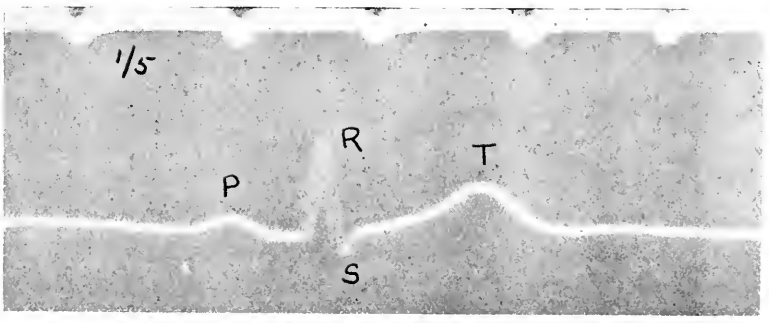

Fig. 3.

An electrocardiogram of a single normal heart-beat. As in all the figures, the upper line is a time marker, showing fifths of seconds. The electrocardiogram consists of variations P, R, S, and T, of which P represents the auricular contraction and R, S, and T the ventricular contraction.

The Physiological Electrocardiogram.

As has been stated, the physiological electrocardiogram is obtained by placing the limbs of the subject investigated in baths of salt solution and connecting these baths to the indicator—the string of the galvanometer. The curve photographed is a complicated one and consists of a number of variations. They have been labelled in a purely empiric fashion with the letters P, Q, R, S and T (figs. 3 and 4).

We may divide the whole curve into two strictly separate portions —P, on the one hand, Q, R, S and T, on the other—and I have termed these separate portions the *auricular and ventricular complexes*

respectively. P is the result of contraction of the two auricles, Q, R, S and T are the outcome of contraction in the two ventricles. Dealing with the ventricular complex (Q, R, S and T), the dips Q and S are usually inconspicuous, while R and T are prominent. It will simplify matters if attention is concentrated upon the more conspicuous variations, P, R and T; of these P is auricular, and R and T are ventricular. The relationship of these variations to the events of cardiac contraction has been definitely ascertained experimentally. The shortening of the ventricular muscle commences a very small fraction of a second after the commencement of R and finishes a small fraction of a second after the subsidence of the broad wave T.

We need not enter into the hypotheses which attempt to explain the constitution of this electrocardiogram, but may rest satisfied at the

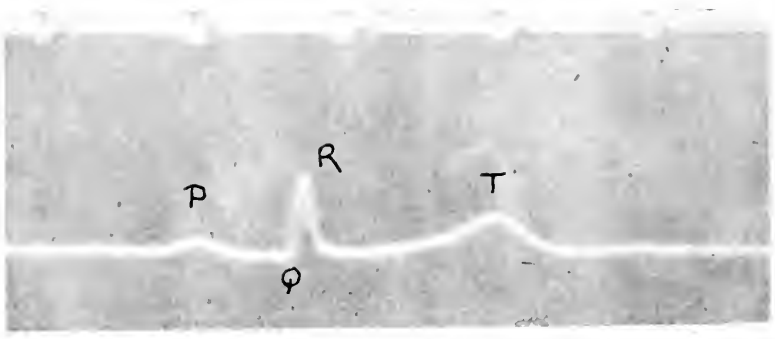

FIG. 4.

A normal electrocardiogram showing P, the auricular representative, and Q, R, and T, ventricular representatives.

present time with the following facts. It represents the electric change in a base-apex lead of a normal mammalian heart, and represents the contraction of the several parts of the cardiac musculature *in a definite order or sequence*. The mammalian heart-beat starts at the junction of superior vena cava with auricle, and the contraction spreads from this point and courses through the auricle to the tissue which joins auricle and ventricle, namely, the auriculo-ventricular bundle. Reaching this tissue the impulse is conveyed along the two divisions of the tract and is distributed through an elaborate arborization and Purkinje network to the ventricular musculature. Let me emphasize the fact that the normal auricular complex (P) indicates in a perfectly decisive manner

the origin of the heart-beat in the neighbourhood of the superior cava ; that is a conclusion which we are forced to accept as a result of experimental observations which I cannot now detail. Let me lay equal stress upon the fact that the ventricular complex (R and T, or Q, R, S and T) indicates a ventricular contraction started by an impulse which reaches it through the *normal field of reception*, namely, the arborization of the junctional tissues. It is only the contraction excited in this manner, i.e., through the physiological paths, which gives rise to a curve of the form described. The importance of these facts will be more obvious at a later stage, and in stating them I am merely elaborating the principle which I stated to you when we considered the simple strip of muscle. The shape of the curve depends upon the direction of contraction, *it consequently depends upon the point of origin*

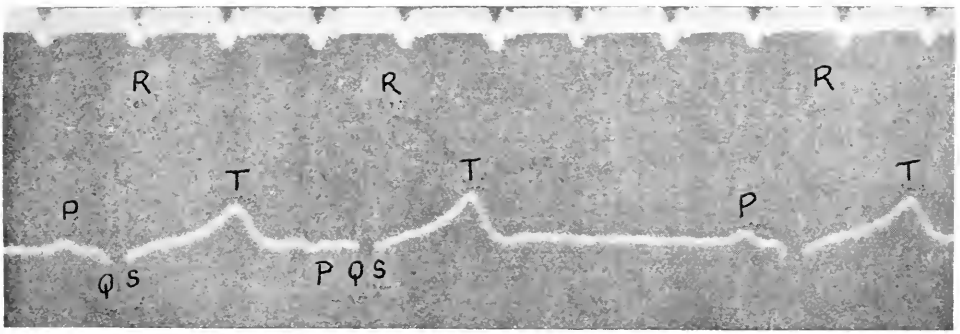

FIG. 5.

An electrocardiogram from a patient showing a premature contraction arising in the auricle. The first beat of the figure shows variations P, Q, R, S and T. They are of normal outline. The second cycle of the figure is the abnormal one. The auricle and ventricle are represented ; the ventricle yields a perfectly normal complex, Q, R, S and T. Directly preceding the ventricular contraction, which is premature, is the representative of the abnormal auricular contraction, P. It may be compared with that of the preceding cycle. The shape of P in the abnormal cycle demonstrates that the auricular contraction has arisen at a point removed from the pacemaker. The third cycle of the figure occurs after a long pause and is normal in every respect. ($\times \frac{2}{3}$.)

of such contraction. Let us take two examples which illustrate this principle, the premature contraction which arises in auricle or ventricle respectively.

The Premature Auricular Contraction.—You are aware that a pulse may be irregular as a consequence of isolated disturbances occurring at

intervals far removed from each other. These disturbances, often spoken of as *intermittences*, are usually the result of *pathological impulse formation* in the heart, and the abnormal impulses may arise in auricle and ventricle, and so far as we know in any part of them. Now, if the premature beat arises in the auricle, it causes and is succeeded by a premature ventricular contraction. In the electric curve it consequently gives rise to an auricular and to a ventricular complex. Except in exceptional instances, which I do not propose to consider, the ventricular complex is a duplicate of the ventricular complex of the normal and rhythmic beats in the same case; and this might have been anticipated, for we know that the impulse generated by the abnormal premature auricular contraction can only spread to the ventricle along the normal paths. The auricular complex of the abnormal beat, on the other hand, has a very variable form,

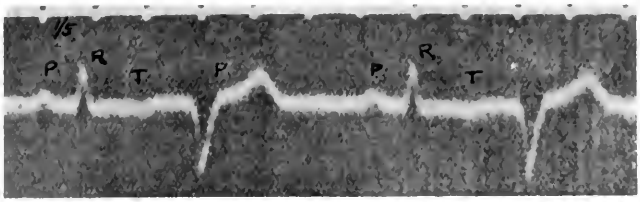

Fig. 6.

From a patient showing premature contractions arising in the ventricle. Each normal cycle is followed by an abnormal cycle. Each normal cycle is represented by the usual variations P, R and T, and is followed by an abnormal cycle representing the ventricular contraction. The abnormal cycle consists of two main variations, one in the downward, the second in the upward direction. The sequential auricular contraction falls in the centre of the premature ventricular contraction. The type of premature contraction shown arises in the apical or left portion of the ventricular musculature. ($\times \frac{2}{3}$.)

and rarely duplicates the normal auricular complex of the same case. The reason for this is evident. The beat has started, not at the normal pacemaker, the junction of superior cava and auricle, but at some other point, and the contraction *in the auricle* has taken an abnormal course (fig. 5).

The Premature Ventricular Contraction.—When a premature contraction arises in the ventricle the abnormal contraction is confined to this chamber. There is no disturbance of the regular auricular rhythm and the P variations are placed throughout at regular intervals. The

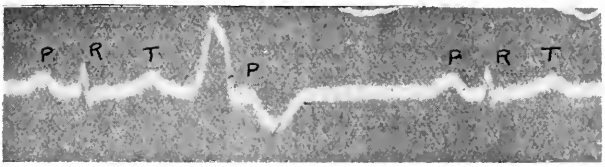

FIG. 7.

A single premature contraction arising in the ventricle. Two normal beats are shown, and are represented by P, R and T variations. The first is followed by an abnormal ventricular complex, of which the first phase is directed upwards and the second downwards. The sequential auricular contraction falls in the centre of the ventricular contraction, and is represented by a wave on the downstroke. This type of premature beat is recognized as one arising in the basal or right portion of the ventricular musculature. ($\times \frac{2}{3}$.)

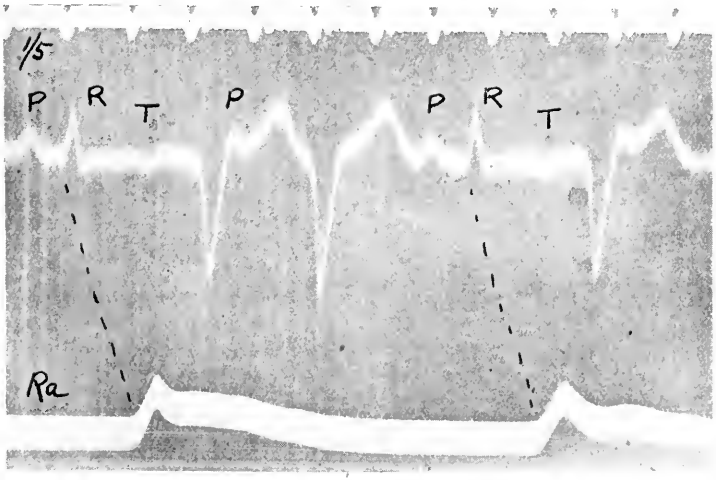

FIG. 8.

Shows premature contractions of the same type as those illustrated by fig. 6. The two figures are from the same case. A radial curve is also included. The premature contractions are more frequent and occur in groups. The figure is given to illustrate two points. First, to show the absence of effect of the abnormal ventricular beats upon the radial pulse; secondly, it is given for the comparison of the outlines of the first two abnormal ventricular complexes. They are not quite similarly shaped, and this is due to the fact that the sequential auricular contraction falls upon the first abnormal ventricular complex, and that the second is free from this complication.

ventricular complex, on the other hand, is no longer of normal form, but varies markedly from it; it may be of many shapes. Usually the normal P variation and the abnormal ventricular complex fall together and superimpose. The shape of the ventricular complex gives a clue to the actual point of the ventricular muscle from which such a beat has arisen; it is possible to obtain approximate experimental duplicates of such curves, but at present the localization is imperfect (figs. 6—9).

In the preceding paragraphs we have considered two of the commonest types of pulse irregularity met with clinically—the premature auricular and ventricular contractions (the auricular and ventricular extra-systoles, as they have often been termed). We may now discuss a rarer form of disturbance.

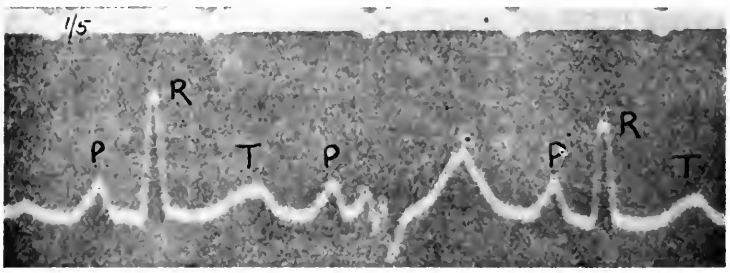

Fig. 9.

An electrocardiographic curve showing a single premature contraction of the ventricle. The first cycle is normal, consisting of P, R and T variations, and so is the last. The sequential auricular contraction, the middle P of the figure, is followed by an abnormal ventricular complex. This abnormal complex represents a ventricular contraction which is not a response to the preceding auricular contraction. This is known from the shape of the curve. It is also evident from the relative shortness of the interval between its commencement and the commencement of the preceding P. From a dog.

A Form of Paroxysmal Tachycardia.—Not infrequently one meets with patients who are the subjects of a well-defined and specific type of paroxysmal tachycardia. The pulse, while beating at a normal rate, becomes abruptly accelerated to rates approaching 150 to 200 beats per minute. The new rhythm is regular, and may be continued for shorter or longer spaces of time (from a few seconds to weeks or even months). It terminates, as it started, quite abruptly; an intervening pause is felt or recorded, and the normal rhythm immediately returns.

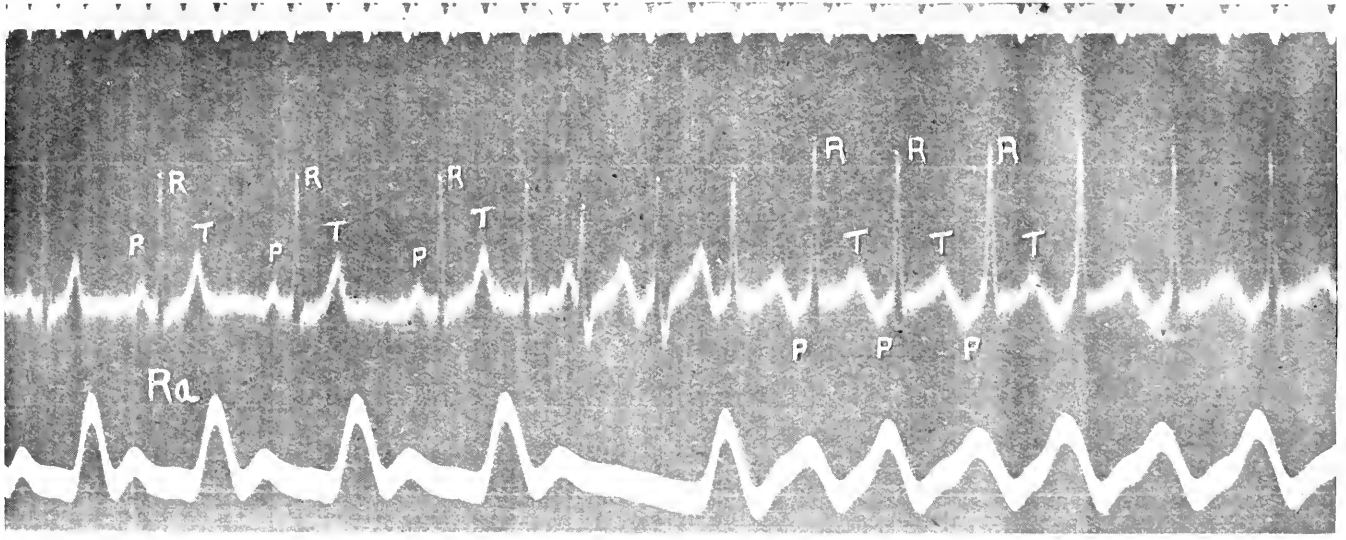

FIG. 10.—An electrocardiogram and radial curve from a case of paroxysmal tachycardia, arising in the lower levels of the auricular musculature. The curve starts with four cycles belonging to the normal rhythm. Each cycle is represented by P, R, and T variations. The paroxysm starts in three curious and anomalous beats, two of which have little effect on the radial curve. When fully established, the paroxysmal beats are represented in the electrocardiogram by a normal ventricular complex, R and T. The shape of these ventricular complexes indicates that the paroxysmal beats have originated from the supra-ventricular portion of the heart musculature. Each ventricular complex is preceded by an inverted P, showing that the contraction in the auricle has taken an abnormal course. It has travelled from below upwards, instead of from above downwards. The paroxysm originated, in all probability, in the neighbourhood of the auriculo-ventricular node.

FIG. 14.—An electrocardiogram, showing the last stage of heart-block; complete dissociation of the auricular and ventricular rhythms. The ventricular beats, R and T, are placed at regular intervals. The rate is approximately 50 per minute. The auricular contractions, P, also occur at regular intervals; the rate is approximately 78. The summits, P, fall with haphazard relationships to the ventricular complexes; frequently they fall with them; in fact, each ventricular contraction of the curve is complicated by the simultaneous occurrence of an auricular systole. The P variations fall with the ventricular complex at various points, and the auricular and ventricular representatives are superimposed one on the other. ($\times \frac{7}{10 \cdot 5}$).

Galvanometric examination of such patients has shown that the fast rhythm of the paroxysm is made up of a number of those beats which we have already examined—namely, premature contractions. Further, it has shown that the paroxysms may arise from a number of foci in the heart muscle, from one or other ventricle, from the junctional tissues, or the auricle itself. The new rhythm has arisen in every case as yet examined from a point in the musculature other than that in which the normal pacemaker lies. This is known by the shape of the electric complexes, auricular or ventricular respectively. In brief, the type of paroxysmal tachycardia referred to is the result of new and pathological impulse formation at an abnormal point. The new rhythms are *ectopic* in origin. It will suffice if a single instance is given (fig. 10).

Auricular Fibrillation.—The commonest of all irregularities of the human heart is that which has been termed *delirium cordis.* It is an

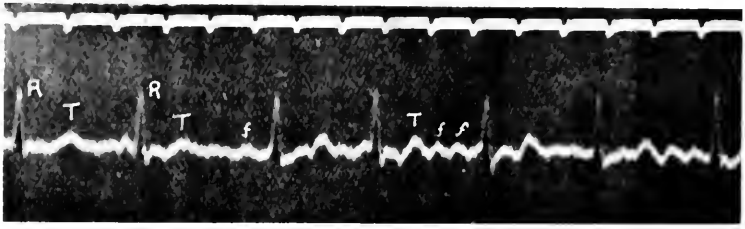

Fig. 11.

An electrocardiogram from a case of fibrillation of the auricle. The ventricular beats are represented by distorted complexes, R and T. The shape of the complexes indicates the supraventricular origin of the impulse creating them. Preceding the ventricular complex there is no regular P variation, representative of auricular contractions under normal circumstances. On the other hand, such P variations are replaced by a series of irregular oscillations, which run throughout the whole curve. They are marked *f f.* These oscillations originate in the auricle, and they produce the distortion of the T variations, which is noticeable in this figure. ($\cdot \frac{3}{5}$.)

irregularity of extreme grade; small and large beats are mixed together in the greatest confusion and at widely divergent intervals. It is especially associated with rheumatic heart disease, and with the widespread and degenerative cardiovascular changes of advancing years.

Galvanometric examination of patients afflicted in this manner has shown that we are dealing with a perfectly definite and a single and specific disorder of the heart's mechanism. It has shown in the most conclusive fashion that the mechanism is one which experimentalists

have termed "auricular fibrillation." Auricular fibrillation is a condition in which the normal and co-ordinate contraction of the auricle, starting from the pacemaker, is replaced by an inco-ordinate condition, in which the auricle remains in diastole, and in which the whole of its musculature is in a state of subdivided activity. It appears as if impulses are initiated in many foci in its walls, and as if these impulses give rise to a turmoil of confused and interfering contractions, no single one of which is effective in expelling the auricular contents. It is from the auricular musculature, thrown into this disorder, that haphazard impulses escape to the ventricle. They escape irregularly, and consequently the ventricular contractions follow each other irregularly. The electric effects in fibrillation may be divided into the two usual components, the auricular and ventricular. The auricular effects consist of a number of rapid and irregular oscillations. One of the striking features of these

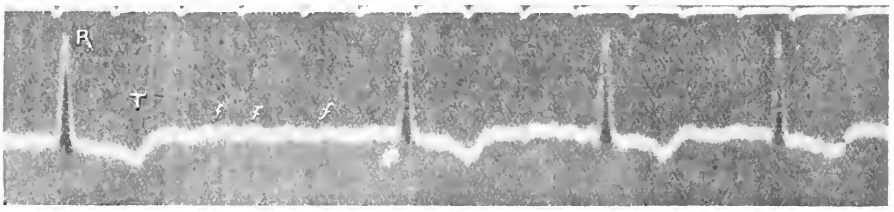

Fig. 12.

An electrocardiogram of a case of auricular fibrillation. The ventricular beats, R and T, are placed irregularly in the curve. The shape of T is noteworthy; it is of the inverted type. The inversion is often held to indicate a severe myocardial lesion. The absence of the normal auricular variation, P, before each ventricular complex is striking. The oscillations which replace the normal representatives of auricular systole are less marked than in the preceding figure, but are quite distinct. ($\times \frac{2}{3}$.)

oscillations is their continuation throughout the whole cardiac cycle, a fact in accord with our knowledge of fibrillation. They completely replace the P variations of the normal rhythm. The ventricular portion of the curve is constituted by complexes consisting of variations R and T, complexes which are placed at irregular intervals. From the shape of the ventricular complexes we know that the ventricular beats have arisen as a result of impulses reaching them along the normal paths; this is as we should expect, knowing as we do that the impulses are generated in the auricle (figs. 11 and 12).

Heart-block.—Another disturbance of the cardiac mechanism, which is by no means so uncommon as was originally supposed, and which is excellently portrayed by electrocardiographic curves, is heart-block. You know that the ventricle receives its impulses from the auricle through the recently discovered tract of tissue known as the auriculo-ventricular bundle. It often happens that disease hinders the conduction of these impulses in varying degree, and such obstruction often leads to very grave circulatory conditions. The several grades of heart-block are as follows:—

(1) The earliest sign of impaired function is manifested by a prolongation of the interval which separates the commencement of auricular and ventricular systoles, the P—R interval, as it is termed, in the electric curve.

(2) At a later stage there may be a failure of response rather than a delay of it; a ventricular response to auricle is completely missed at intervals.

(3) Further stages consist in more frequent ventricular silences, so that the auricle beats two, three, or more times as frequently as the ventricle.

(4) The final stage is one of complete dissociation of the auricle and ventricle, each beating regularly and of its own accord, independently and at different rates (figs. 13 and 14).

In the preceding paragraphs I have given you a few of the more simple forms of cardiac disorder in illustration of the galvanometric method, and I do not propose to exemplify the subject further. But it should be understood that the knowledge which the instrument affords us does not end here. I have not touched at all upon a wide field—the examination of hearts in which the ventricle beats regularly and in which the sequence is normal. It is perhaps premature to speak of them in a paper which merely pretends to outline the subject; but it is only fair to the instrument to state that it promises well in this direction. Those who are specially studying the electrocardiogram see that in the near future it may permit of the diagnosis of the auricular hypertrophy of mitral stenosis, and, as a consequence, the valve lesion itself, at so early a period of the life-history of the disease that the ordinary physical signs are wanting. There is also very suggestive evidence that it will supply us with more certain means than we enjoy at present of ascertaining and dissociating hypertrophy of one or other ventricle. These questions may be left for a future occasion.

I may conclude by summarizing the present position of the galvanometer in its relationship to the practice of medicine.

A Summary of the Relationship of Electrocardiographic Work to the Practice of Medicine.

An estimate of the practical value of a single method of physical examination is at no time easy, and it is especially difficult when we deal with a method which is still in its infancy. In offering my own impressions of the relationship of the electrocardiographic methods to the practice of medicine, let it be understood that I give them as they appeal to me at the present time and after several years' study.

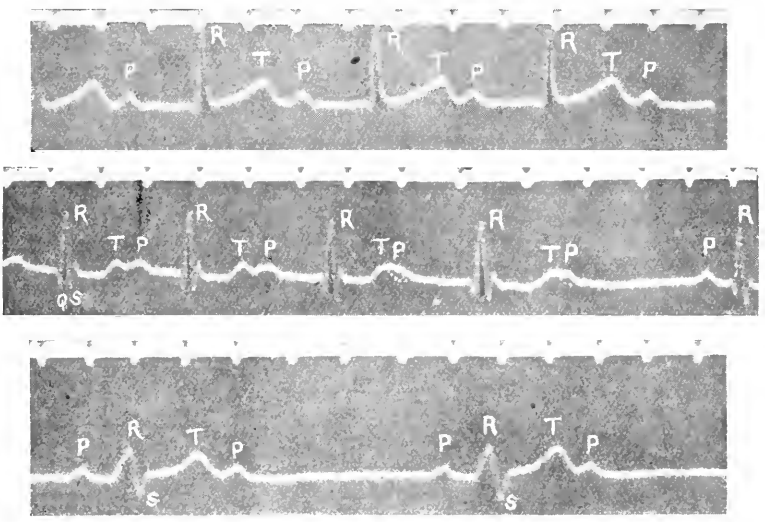

Fig. 13. *i*, *ii* and *iii*.

Three clinical curves to illustrate stages of heart-block. In fig. 13, *i*, the heart is beating regularly and the sequence is normal, in so far as each ventricular contraction, R and T, is preceded by an auricular contraction, P. The curve is nevertheless abnormal; the P—R interval is increased from the normal 0·12 to 0·17 sec. up to 0·3 sec. Fig. 13, *ii*, is from a case of mitral stenosis on digitalis. It is an example of dropped beats. The ventricular complexes are represented by the variations, Q, R, S and T, and in the early stages of the curve each ventricular beat is preceded by an auricular contraction, represented by P. It is to be noted that as the curve proceeds the P—R interval gradually increases until P falls back and is superimposed upon the preceding variation, T, of the ventricular contraction; the interval, P—R, for this cycle is nearly 0·3 sec. Up to this point the auricular impulse has had increasing difficulty in reaching the ventricle; the dropped beat is the final expression of this hindrance. At the end of the figure the next response of ventricle to auricle is shown. After the long rest the P—R interval decreases markedly. Fig. 13, *iii*, is from a case of heart-block in which the ventricle is responding to alternate beats of the auricle. The auricular complexes, P, are twice as numerous as the ventricular complexes, R, S and T. The curve is remarkable in that it shows a prematurity of alternate P variations, an early occurrence of the auricular contraction immediately following each ventricular contraction. The explanation of this phenomenon is unknown. ($\times \frac{2}{3}$).

I should do wisely, I think, if I placed in the foreground, not the method itself, but the general conclusions which have been arrived at as a result of its employment, confining attention to those facts which have an immediate influence upon our conceptions of pathological conditions. Regarded from this point of view, our attention concentrates upon two conditions, which are usually referred to as *delirium cordis* and paroxysmal tachycardia respectively.

As a result of investigations carried out with the galvanometer, we are now in a position to assert in the most positive fashion that what has been termed in the past delirium of the heart is, in fact, a condition known to experimentalists by the name "fibrillation of the auricle." The clinical importance of recognizing this disorder of the cardiac mechanism can scarcely be exaggerated. It is directly accountable for 50 per cent. of all irregular pulses as they are encountered in a general out-patient department, and for an even higher percentage in the wards of a general hospital. In patients who are the subjects of heart affections attributable to a rheumatic infection, and in elderly patients who succumb as a result of progressive sclerotic myocarditis, the final breakdown is often, if not generally, heralded by the onset of this curious, distinct, and easily recognizable mechanism. The importance of identifying it is obvious, not only on account of its universality, its profound influence upon the life-history of the heart affected by it, but equally because, being a mechanism *sui generis*, it reacts to cardiac drugs in a specific manner. This is not the place in which to refer to the disorder in greater detail, but only to emphasize the imperative need of an acquaintanceship with the condition, and to claim for the galvanometer its final isolation and analysis.

I pass to the second condition, namely, paroxysmal tachycardia. Formerly it was regarded as of obscure origin, and frequently attributed to an affection of the cardiac nerve-trunks or their connexions. Now we possess clear evidence that cases which fall within this category may be placed in several distinct classes. Of these classes, two are peculiarly striking. In the one, the paroxysms of tachycardia consist of temporary crises of auricular fibrillation. There are paroxysms of rapid heart action, in which the ventricular beats follow each other irregularly. In the other form, which I have already briefly described, the paroxysms depend upon the awakening of new impulse formation in the heart musculature, and in some fixed point at a distance from the normal seat of impulse formation. It has been ascertained that the attack is the result of a temporary dislocation of the site of the *primum movens;* or, perhaps, as it may be expressed more correctly, it is caused by the

extinction of the rhythm of the normal pacemaker at the development of a new and more rapid rhythm in a point some distance removed from that which originates the normal rhythm. For the elucidation of these facts we are indebted to the new method. And, it may be stated in parenthesis, that our knowledge of the actual site of origin of the normal mammalian heart rhythm is largely referable to the same source. The normal rhythm of the heart arises, as we now know, from a small area of the right auricle immediately abutting upon the entrance of the superior vena cava.

I have placed these additions to our general knowledge in the forefront of the account rendered by the galvanometer, because they must necessarily and immediately modify our conception of, and our attitude towards, many clinical conditions, and because they form additions to the chapter of cardiovascular pathology which we can ill afford to neglect. Even a summary perusal of the multitude of the newly acquired facts furnished by the instrument has been impossible in the time at our disposal, and in this brief account these isolated examples have been stressed, not only because I am in a position to speak with a first-hand knowledge of them, but because they appeal to me as constituting generalizations, which cannot fail to receive general clinical application in the near future.

In closing an outline of the general conclusions in respect of which the new method debits us, we cannot lose sight of its important bearing upon other and more strictly clinical methods of examination. It may be stated that the galvanometer has already substantiated the great bulk of the facts previously acquired by means of the polygraph. It is true that it has at times led to conclusions at variance with previous conceptions, but the point which should be specially emphasized is that the galvanometer shows in the most unequivocal manner that we are fully justified in accepting the present-day interpretation of the vast majority of venous pulse records; and that the older method yields analyses of the heart mechanism which are almost always upheld if submitted to the arbitration of this new instrument; and the importance of this conclusion will be more evident when it is remembered that the galvanometer is essentially a laboratory instrument, while the polygraph accompanies the clinician to the bedside of his patient. From this point of view the polygraph may be regarded as a go-between, obviating the necessity of transplanting a cumbersome apparatus.

Of the more immediate benefits conferred by the instrument I speak more hesitatingly. The size, weight, and cost of the galvanometer and its fittings materially restrict its sphere of usefulness. It has to be

maintained as a fixed installation, and it is difficult to see how it can ever leave the immediate precincts of the laboratory or hospital. These disabilities are reduced to some extent by the possibility of bringing a relatively large area within its immediate working sphere. The instrument may be connected by properly insulated wire to any ward or room within a convenient range. A single outfit will consequently supply a single institution or several institutions in its immediate vicinity. As a part of the equipment of a modern hospital or physiological laboratory it is already almost a necessity. Once installed it gives a ready and infallible analysis of the sequence of contraction of the cardiac chambers. A few minutes (three or five) places the clinician in full possession of all the necessary data for the analysis of an arrhythmia in all but exceptional instances, and the data are of the most accurate nature. In several respects it presents material advantages over the polygraphic method. Its superiority as an instrument of precision is unquestioned, a quality which is dependent upon the directness of the method. A venous record is an expression of an effect of the heart upon venous inflow; the electric curve is an expression of the heart-beat itself. A second and considerable advantage consists in the ease with which the majority of the records are read: polygraphic curves often require minute and often tedious measurement; the majority of electrocardiograms may be read at first sight. In the third place it gives valuable information, not only as to the instants at which auricle and ventricle contract, but as to the direction which the contraction waves pursue in individual chambers, and consequently as to the points at which such contraction waves arise in the chambers. In brief, it is a weapon which has no equal for precision where an analysis of the cardiac mechanism is required; it takes precedence of all other methods where evidence is conflicting; the information obtained is secured with a minimal expenditure of time.

The comparison of one method of physical examination with another is always difficult, but restricting comparisons to hospital patients, I have little hesitation in stating that in the routine examination of the heart patients the galvanometer method affords, or will afford in the near future, information of equal or greater value than any other single method at our disposal, be it instrumental or subjective. It must be allotted at least an equal place with percussion and auscultation, with sphygmomanometry and radiography; and in this respect it has this to be said for it, that the information it offers it offers definitely, the information it withholds it withholds as definitely; it is, in fact, a method of exactitude, a method of precision.

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MODERN ENGLISH CARDIO-VASCULAR TEACHING: A REJOINDER

By THOMAS LEWIS[1]

(University College Hospital Medical School).

With Plates 28 and 29

It is customary for those who make a special study of graphic records to give, when explaining their figures, interpretations of the curves which appear to them in closest accordance with previously published facts, and with their own experience of similar curves.

In giving dogmatic interpretations of curves, a conscientious writer confines himself to such interpretations as he feels will meet with the general approval of those who are alone fitted to judge of their correctness. I speak of those who are actively engaged in the collection of facts. He is not called upon to repeat, in each instance, the evidence which is well known to such students, though it may be unknown to the casual inquirer, but only to give a sufficiency of evidence to make his whole communication rational. It so happens that any who may chance upon isolated examples of curves, the interpretation of which appears to stand in contradiction to their own preconceived ideas, are entering upon a hazardous course when they venture to criticize before rendering themselves fully conversant with the facts.

It is not my purpose to follow Dr. Brockbank from paragraph to paragraph, or to show, as could be shown, the tenuity of one argument after another as they are advanced in his article. It is not the duty of a worker to defend the writings of a school to which he may be thought to belong; but it is his right to vindicate those personal interpretations of his published curves, which have been called in question.[2] This I shall proceed to do.

The first tracing to which I wish to refer is the first figure of Dr. Brockbank's article (republished from *Heart*, 1909–10, i. 48, Fig. 1). It is again published, as Fig. 1 of this communication. Dr. Brockbank says of it (this Journal, 1910, iii. 349):—

'Here are jugular and radial pulse records from a patient with a pulse rate of 187, and it is said that the *a–c* interval was *equal to or slightly more* than 0·02 sec.—certainly it measures this by the time marks. It will be seen that the *a* wave is very prominent, and if perpendiculars be drawn from its origin and from its summit they will be found to enclose a space

[1] Working under the tenure of a Beit Memorial Research Fellowship.

[2] And in so doing I shall answer the criticisms, not only of the interpretations of my own curves, but also of many others which are discussed in Dr. Brockbank's paper.

equal to full 0·20 sec. So here we have a figure showing that out of 0·3 sec. occupied by the whole of the cardiac cycle, not only does the *a*–*c* interval equal 0·2 sec. or more, but auricular systole itself extends throughout the whole of this period of time, and that is more than twice the time that is occupied by ventricular systole. In other words, whilst the duration of ventricular systole is normally about three times as long as auricular systole, here it is half as long, or one-sixth of its normal relative duration as compared with auricular systole.'

Dr. Brockbank concludes that if the interpretation of the curve is correct the auricular is of twice the duration of ventricular systole, and appeals to the incredulity of his reader on this ground. But on what evidence does he base his contention?

First, it is based upon a calculation of the length of auricular systole. The measurement is made by Dr. Brockbank *by drawing perpendicular lines from the origin and summit* of the wave *a*. Now let us assume for the sake of argument that the base and summit of *a* are representative of the times of onset and offset of systole in the auricle, an assumption which, though knowing *a* to result from auricular systole, I never have made. Is the measurement which Dr. Brockbank makes justified? It is anything but justified, and entails an

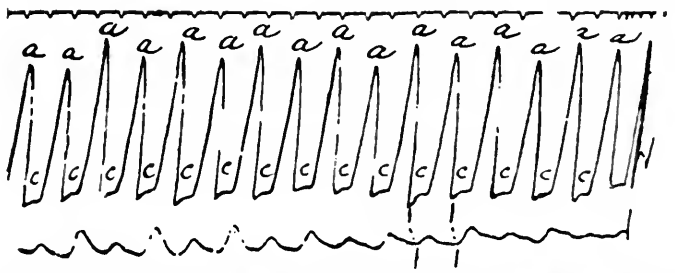


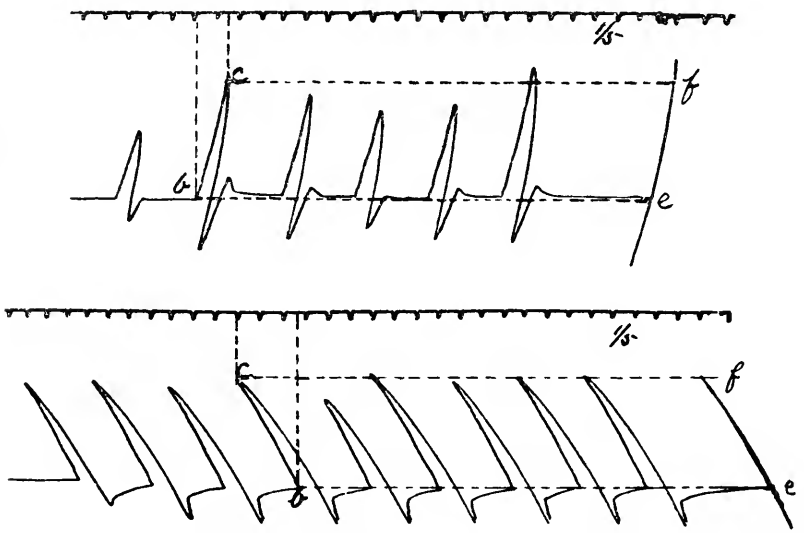
FIG. 1. A polygraphic curve from a case of paroxysmal tachycardia, in which, while ventricle is responding to auricle, a given auricular systole coincides with the end of the preceding ventricular contraction. The first curve criticized by Dr. Brockbank.

extremely elementary blunder. The curve is written from left to right by a lever, the pen of which moves through the arc of a circle. Any transference of times from points of the curve which lie at different levels on the paper has to be corrected against the index-mark which is shown at the end of the curve, and this index-mark is not perpendicular. The general direction in which the pen inclines, in writing the *a* waves measured, is of first importance if the smallest approach to accuracy is to be obtained in measurement. Let me take an extreme case. I have drawn two series of waves with a polygraphic lever on separate strips of paper, on each of which the time is marked in fifths; and I have lettered the waves *b* and *c*. Each strip also shows its respective index-mark, but they are at different inclinations. The waves in Figs. 2 and 3 are of approximately the same dimensions. Following the example of Dr. Brockbank, let us draw perpendiculars from *b* and *c* to the time marker in each curve. We know at the outset that the actual time distance between *b* and *c* is approximately the same in the two curves, for they were drawn in a similar manner. In Fig. 2 it measures, by the method of perpendiculars, $\frac{1 \cdot 4}{5}$ sec. (the

time marker is in $\frac{1}{5}$ sec.). In Fig. 3 it is a minus quantity; the actual measurement stands at $-\frac{2{\cdot}6}{5}$ sec. According to the angle at which your lever writes, you make the length b–c what you please. How is the true measurement of the time interval between points b and c to be obtained? By very simple means. It is found by subtracting the distance c–f from the distance b–e (Figs. 2 and 3).

The true measurement of the time interval between the origin and summit of the a waves in Fig. 1 is somewhat less than 0·1 second, or less than half the distance given by Dr. Brockbank.

Let us turn to the second measurement of the same writer. He states that of 0·3 sec. occupied by the whole cardiac cycle, 0·2 sec. is taken up by the



FIGS. 2 and 3. Two series of curves drawn with the polygraph. The curves are quite roughly drawn, but are sufficient for purposes of illustration. At the end of each series, the curved index-marks are shown. It will be observed that they are inclined in different directions. The general inclination of the waves is the same as that of the corresponding index-mark. To illustrate the fallacy of measuring the duration of waves by drawing perpendiculars to the time marker.

auricular systole. And he infers therefore that ventricular systole cannot occupy more than the remainder, namely 0·1 sec. In taking this second step, Dr. Brockbank utilizes a time measurement (e. g. 0·2 sec. for auricular systole) which is absolutely invalid. If any measurement had been taken it should have been, as we have seen, 0·1 sec. The relationship of what he chooses as measurements of auricular and ventricular systole would then have stood at 0·1 sec. for auricular and 0·2 sec. for ventricular systole respectively. In brief, whereas he infers that my interpretation shows auricular to be twice the duration of ventricular systole, he should, in taking the second step, have allowed the reverse relationship. But this does not complete a description of the errors in the complete argument. It is assumed that as the pulse rate is 187, the length of the whole of each regular cardiac cycle is 0·3 sec. The value of the whole cardiac cycle is

apparently obtained by the not very exact calculation $\frac{60}{187} = 0{\cdot}3$ (I note in passing that the inexactitude tells in favour of Dr. Brockbank's thesis). But as a matter of fact the foundation of the whole argument is fallacious. It is quite beyond the bounds of possibility to calculate the length of 'a whole cardiac cycle' by an estimate of pulse rate. All that can be deduced in regard to the lengths of systole of auricle and ventricle from a pulse rate of 187 is that ventricular systole occupies less than 0·32 seconds. And the reason for this is obvious, for it may chance that auricular and ventricular systole coincide. I illustrate

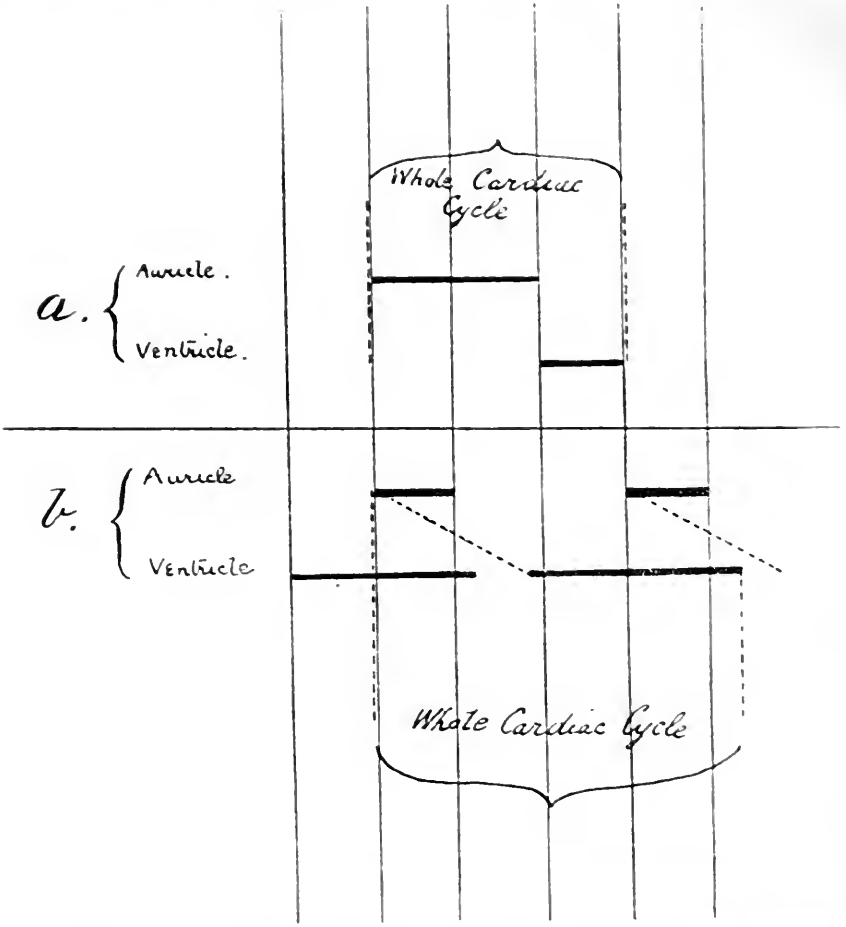


FIG. 4 *a* and *b*. Two figures illustrating interpretations of the mechanism portrayed by Fig. 1. The vertical lines are separated by time intervals of 0·1 sec. The figures show the fallacy of calculating the length of the 'whole cardiac cycle' from the pulse rate.

this point by the accompanying diagram. Fig. 4 *a* depicts cardiac cycles in which the relationships of auricular and ventricular systoles is as Dr. Brockbank would have them. Fig. 4 *b* depicts a relationship such as I maintain is far more probable for the case under consideration. And Dr. Brockbank deliberately neglects this question of coincidence of systoles in referring to my figure, although such coincidence is spoken of in perfectly distinct language in my original paper (p. 49).

I submit that instead of the statement that 'out of 0·3 sec. occupied by the whole of the cardiac cycle, not only does the *a–c* interval equal 0·2 sec. or more, but auricular systole itself extends throughout the whole of this period of time, and that it is more than twice the time that is occupied by ventricular systole', Dr. Brockbank should have written, 'the auricular systole occupies 0·1 sec. or less,[3] and as the ventricular cycle cannot be shown to be shorter than 0·25 sec., it is beyond my power to demonstrate from the original interpretation of this figure that auricular systole is more than $\frac{1}{2}$ to $\frac{1}{3}$ the length of ventricular systole.' The deviation between actual and justifiable statement is sufficiently conspicuous to require no further comment.

I pass to the second of my published curves, the interpretation of which is the subject of Dr. Brockbank's remarks. It stands as Fig. 6 in his paper, and the original will be found in this Journal, 1908–9, ii. 359 (Fig. 6). I reproduce it here again, as Fig. 5.

Now I maintain in the first place that it is illegitimate to separate a tracing from its companion curves, and it happens that the isolation of this particular example materially detracts from its value. The curve in question is one of a group of seven published from the same case, and of the two curves criticized (Figs. 6 and 7 of the original paper) Fig. 6 is alone republished by Dr. Brockbank. I republish Fig. 7 also (it stands as Fig. 6 of the present paper).

In regard to these two figures, Dr. Brockbank writes (pp. 353–4):—

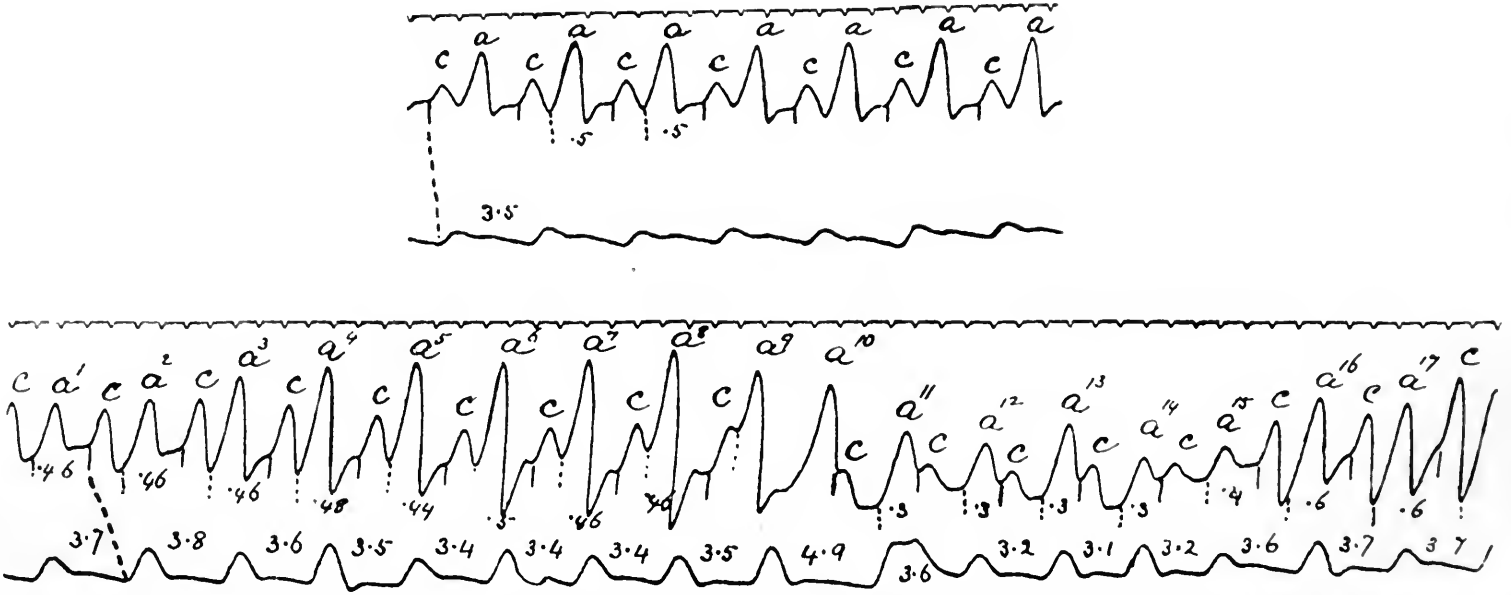
'Another illustration of the passing over of waves which, occurring at the proper time, are possibly, if not probably, due to auricular systole, occurs in a paper by Lewis in this Journal on "Irregular Action of the Heart in Mitral Stenosis and the inception of Ventricular Rhythm". In Figs. 6 and 7 the wave marked *a* and attributed to auricular systole, without any obvious reason, is, I suggest, wrongly marked. In Fig. 6[4] there is a distinct wave at the proper time for that due to auricular systole and following, by as much as 0·30 sec. in some beats, the wave attributed in the tracing to auricular systole. In Fig. 7[5] again the wave marked *a* precedes by 0·25 sec. a distinct wave at the proper time for auricular systole.'

Now take the first curve referred to, Fig. 5 of this paper. I recognize that it would perplex me to show on *the evidence of this curve alone* (and it is the only curve republished by Dr. Brockbank), and to an uninitiated reader, that the wave marked *a* is the true representative of auricular systole. But I shall have no difficulty in showing that such is the case if I am allowed to refer to other curves taken from the same patient. Fig. 6 was taken at the same sitting and was published at the same time. There are waves in this figure of a similar nature. I have marked certain waves a^1–a^{17} respectively and I direct attention to a^2 and a^{16} especially. I think there can be no doubt, even amongst the most sceptical, that the waves marked a^2 and a^{16} in Fig. 6 have been caused by a similar mechanism to that which produced the waves marked *a* in Fig. 5.

[3] Personally I will not state its length at all.

[4] Fig. 5 of the present paper.

[5] Fig. 6 of the present paper.



FIGS. 5 and 6. Two criticized curves originally published in this Journal. Fig. 5 was republished in Dr. Brockbank's article and stands as Fig. 6 of his paper. The curves were originally described to demonstrate the presence of heart-block in the case from which they were obtained. The heart of the patient has recently been examined and shows extensive damage to the auriculo-ventricular bundle. They are companion curves and are fully described in the text. They illustrate the danger of separating such companion curves. The one curve explains the other.

But in Fig. 6 a^2 and a^{16} stand in definite relationship to the full series of a waves shown. They fall at approximately equal distances throughout the whole curve, though they vary in form. It is the relationship to the preceding ventricular systole, represented by c in the upper or venous curve, which shows variation in time, and this, as we shall see, is the cause of the variation in the form of the whole series of waves marked a in the curve considered (details which are fully entered into in my original paper and which I must perforce repeat). My contention is that the waves marked a in the curve are due to auricular systoles. Take a^{11} and a^{12}: they are *prominent* waves immediately preceding the c's, the representatives of the onsets of corresponding ventricular contractions. They stand in the presystolic periods of the jugular curves, and there is no factor in operation in the heart, other than auricular systole, and at such times, which is capable of giving rise to waves of this kind. They are not in any way attributable to a ventricular systolic event, for ventricular systole has terminated before each of such waves commences. And if this could not be shown in the case of a^{11} and a^{12}, it would be obvious in the case of a^{10}, which stands, as the radial curve shows, at the end of a relatively long diastole. Now a curious transition is shown between a^{11} and a^{17}. The interval between a^{11} and its corresponding or succeeding c is 0·3 sec.; and this interval is maintained for four beats. At a^{15} there is further prolongation of the interval (the normal length is 0·2 sec. or less) to 0·4 sec. and in the succeeding beats the value reaches 0·6 sec. Yet the waves marked a are approximately regular throughout. The variation in intervals is an accompaniment of a movement of a given ventricular contraction (c wave) away from the wave a of the corresponding cycle. And this delay of ventricular contractions is necessarily followed by a gradual approach of a given a wave to the preceding ventricular contraction. Now what is the rational interpretation of these events? It is that the a waves are due to auricular systole and that the auricular systoles are the cause of the succeeding ventricular contractions, but that for some reason or other there has been an increasing impediment to the passage of the impulses supplied to the ventricle by auricular contractions; thus, as the curve proceeds, the auricular systole and the corresponding ventricular response become further removed from each other. Now this interpretation is in complete accord with a host of researches of the most careful kind, and well known to special students of the subject. But let us continue to examine the proposition on its own merits, in respect of the curves shown. An examination of waves a^{11} to a^{17} leads us to the conclusion that there is a defect in the conduction of impulses from auricle to ventricle. This conclusion is in absolute agreement with the interpretation of the events surrounding a^9 and a^{10}. a^9 is followed by no radial beat, neither is there a c wave following it in the phlebogram.[6] On the other hand it is associated with an increased pause in the radial pulse. This pause is attributed to

[6] The venous lever is not writing directly above the radial curve but somewhat to the left of it. Corresponding arterial pulsations are joined by a dotted line at the beginning of the curve.

a 'dropped beat', an exaggeration of the impediment to the passage of impulse already noted, an exaggeration which culminates in a complete failure of response. Lastly, we may revert to the question of the variation in height of the waves marked *a*. This variation receives complete explanation, if it is assumed that the *a* waves are the result of auricular systoles. For the height of a given wave is in proportion to the calculated pressure at the tricuspid ring at the moment of its occurrence. The nearer the approach of an *a* wave to the preceding *c* wave, the higher it is: and this is so for the reason that the auricular contraction falls further and further into the preceding ventricular systole, and that instead of the auricle emptying into the ventricle its contraction tends to raise venous volume. The phenomena of coincidence of auricular and ventricular contraction, and exaggeration of the wave in the phlebogram with which such coincident contraction is associated, have received accurate experimental study by several observers, and are perfectly well recognized. It is beautifully illustrated in the two venous staircases shown in Fig. 6. (The exaggeration of a^{10} is the outcome of the increased pressure in the ventricle as the result of blood accumulation in it during the long diastole.)

Now I contend that this interpretation of Fig. 6 is absolutely in accord with previously published *facts*, that the proposition that the *a* waves are the result of auricular systoles constitutes the only rational interpretation of the curve, and this interpretation would be unhesitatingly adopted by any one sufficiently acquainted with polygraphic work. The reading of the figure gives unquestionable evidence of the presence of heart-block, evidence in every way compatible with our knowledge of heart-block. But if the *a* waves of Fig. 6 are due to auricular systoles, so are also the *a* waves of Fig. 5, for they may be traced continuously in the original curves from one tracing to the other. In Fig. 5 the interval *a*–*c*, as marked, is increased (from the normal 0·2 sec.) to 0·5 sec.

Dr. Brockbank's chief difficulties in regard to Fig. 5 are, first, his unwillingness to admit the possibility of a widened conduction interval, and secondly, his failure to appreciate the possibility of the coincidence of an auricular with the preceding ventricular contraction.

To each of these questions I shall return subsequently. At the present time let it be noted that I published these two figures with a specific object, namely, to demonstrate the presence of impairment of impulse conduction between auricle and ventricle, a demonstration which Dr. Brockbank will not allow to have been completed. Now impulse conduction from auricle to ventricle occurs, as my readers will know, through a narrow bridge of tissue uniting auricle to ventricle, the auriculo-ventricular bundle. The sequel speaks for itself. As a result of an examination of these curves, I was of opinion that the functions of this bundle were deficient, and the curves were published as evidence of the contention. The patient from whom the curves were taken died many months ago,[7] and Professor Woodhead reports that the bundle in question is invaded by a conspicuous lesion. So much for the actual curves and the

[7] The heart's mechanism remained practically unaltered until death occurred.

conclusions to be drawn from them. I turn to a further demonstration of two facts: (1) that while ventricle is responding to auricle, the auricular systole may coincide with the preceding ventricular contraction, and (2) that a prolongation of the interval between *a* and *c* waves in the jugular pulse is an invaluable and sufficiently accurate guide to the interval between the onset of auricular and ventricular systoles in the heart itself.

The first demonstration is necessitated, because I utilize the argument in the discussion of Figs. 1, 5, and 6, and because Dr. Brockbank is disinclined to admit it; he neglects the possibility where he calculates the relative duration of auricular and ventricular systoles (cf. Fig. 4 and discussion relating to it).

The second demonstration is necessitated while Dr. Brockbank, in speaking of heart-block, writes (on p. 359):—

'Such cases[8] undoubtedly exist, but there is no definite clinical evidence to show that the *a-v* bundle ever passes on stimuli at a pathologically slow rate, let alone at such an abnormally slow rate as it is said to in Griffith's and Lewis's cases.

A prolongation of the *a-c* interval in hearts beating 60 or 40 or less is quite conceivable in cases of mitral stenosis or disease of the *a-v* bundle, without there being any alteration at all in the normal sequence of events of a cardiac cycle.'

Now whatever be the merits or demerits of the polygraphic method, I think that even Dr. Brockbank will be prepared to admit that we have in the electro-cardiographic method a certain means of identifying the approximate times of onset of auricular and ventricular systole. It is a method of recognized accuracy and is in no way open to criticism on the score of variation in transmission intervals. After a large experience of both methods, I have no hesitation in stating that the galvanometer has confirmed all the main and generally recognized facts which have been won by the polygraph; these new records have completely substantiated the value of the older method.

When I enter upon a demonstration of the two propositions cited above, I do so under protest. I say emphatically that both these propositions were established before the modern electro-cardiogram was heard of.

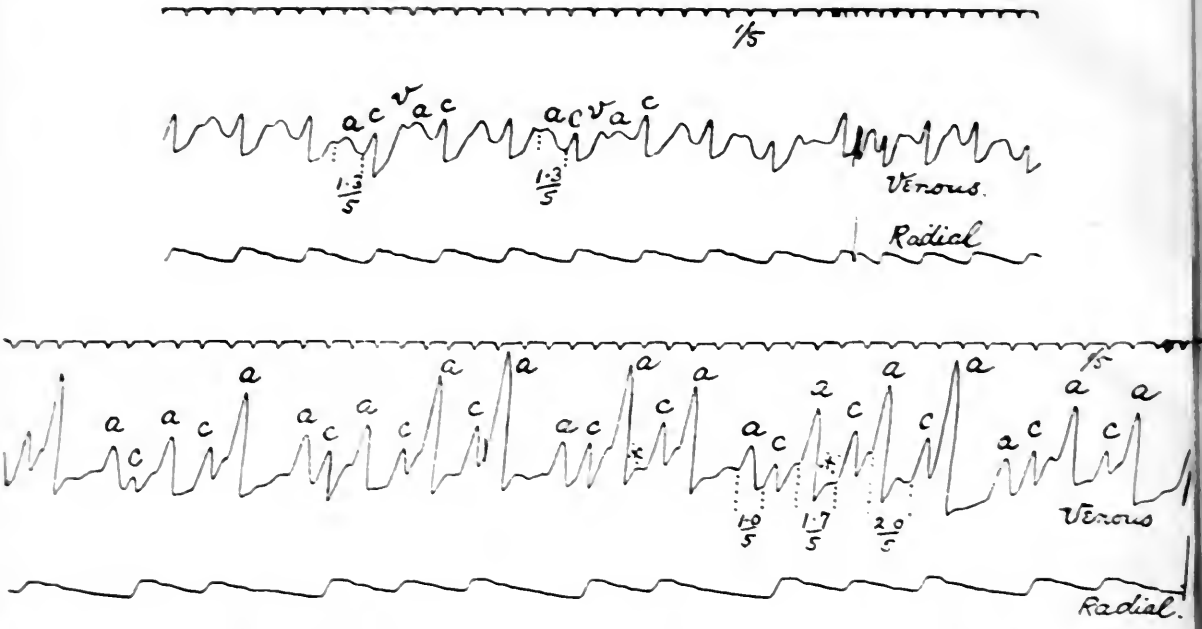
The fact that a prolongation of the auriculo-ventriculo-systolic interval may occur has been fully established experimentally, and I should have no difficulty in quoting abundantly to this effect. But let us confine ourselves to the mammalian heart with which we are dealing. It will suffice if I quote from Erlanger's classical paper on this subject. Speaking of the dog's heart, he says (*Journ. of Exper. Med.*, 1906, viii. 57):—

'(1) Upon cautiously tightening the clamp, the first obvious effect may be an increase in the period intervening between the beginning of an auricular contraction and the beginning of the ventricular contraction, *the intersystolic period*, of the same cardiac cycle. The duration of the intersystolic period may then gradually increase in the successive cycles until eventually the ventricles fail to respond to one of the auricular contractions (Fig. 20, G). Immediately following this ventricular "silence" the intersystolic period again becomes short and it again increases,' &c.

But it is my desire that the reader should have the actual facts before him. In Figs. 9 and 10 I reproduce electro-cardiographic curves, taken from two dogs

[8] Cases of heart-block.

during periods of asphyxia (Lewis and Mathison, *Heart*, 1910–11, ii. 47, Figs. 2 and 3). The normal electro-cardiogram consists of three chief summits, P, R, and T, and in regard to these peaks it has been shown beyond dispute that P represents auricular and R and T ventricular contraction. The two figures, which are republished, show partial heart-block. Each ventricular complex (R, T) is preceded by an auricular peak, P, but at very varying time intervals. And in two places in the first figure (Fig. 9) and in three places in the second figure (Fig. 10) a P summit stands isolated. The responses to these auricular beats are 'dropped'. After each dropped beat there is a prolonged ventricular



FIGS. 7 and 8. Two polygraphic curves from a case presenting signs of regurgitation through the mitral orifice. They show prolongation and variation of the *a–c* interval: and are published for this purpose. In Fig. 7 the *a–c* interval is $\frac{1·3}{5}$ sec. In Fig. 8 there are 'dropped' beats.

pause, at the termination of which the interval P–R (a measurement of the auriculo-ventriculo-systolic period) is relatively short. With the succeeding beats it shows gradual prolongation, i.e. the auricular impulses are transmitted, with ever increasing difficulty, up to the point where response fails. The events in Fig. 9 are as follows:—P–R interval 0·12, 0·14, 0·17, dropped beat. In Fig. 10 they are P–R interval 0·13, 0·18, 0·30, dropped beat.

Again, note the position of the P waves, which are succeeded by long intervals: *they fall within the limits of preceding ventricular systoles*, for ventricular systole ends somewhat later than the point at which the broad T wave reaches the base line.

Let us turn to the final demonstration, for Dr. Brockbank, though prepared to quote experimental evidence, specially mentions the *clinical* evidence.

Figs. 7 and 8 were taken from a single patient,[9] a case of exophthalmic goitre with enlargement of the left ventricle and mitral regurgitation. They are polygraphic curves and are selected from a series taken from this patient. The curves as a whole showed, from day to day, a gradual and uniform improvement in auriculo-ventricular conduction, which was considerably damaged when the patient was first seen.

The phenomena noted in this patient were as follows:—

First day of observation: ventricle responding to each second, and occasionally to each third auricular contraction only.

Second day: ventricle responding to each second auricular contraction, and occasionally to successive impulses.

Third day: ventricle responding to successive auricular contractions, with occasional dropped beats.

Fourth and subsequent days: prolongation of the auriculo-ventriculo-systolic interval; no dropped beats.

I begin with the later curves. Fig. 7 is from a prolonged tracing in which the *a–c* interval measures $\frac{1\cdot3}{5}$ sec.[10] It is given for comparison with a simultaneous polygraphic and electric curve taken on the preceding day. This is shown in Fig. 11. In the electro-cardiographic and venous curves regularly placed waves are seen:—

	Auricle	*Ventricle*
Electro-cardiographic	P	R, T
Polygraphic	*a*	*c*, *v*

In the electro-cardiographic curve the P–R distance, in the venous curve the *a–c* distance, is taken as an index of auriculo-ventricular conduction. Now the curve reads from left to right, and *c* stands approximately $\frac{0\cdot6}{5}$ sec. to the right of R and *a* approximately $\frac{0\cdot6}{5}$ sec. to the right of P. This interval is due in part to the conduction time of the venous waves to the neck, and in part to the transmission time of the recording apparatus (calculated at the time at $\frac{0\cdot2}{5}$ sec.).[11] The figure shows a series of *a–c* and P–R interval of $\frac{1\cdot4}{5} - \frac{1\cdot5}{5}$ in duration. The divergence between *a–c* and P–R is in no instance greater than $\frac{1}{50}$ sec., a divergence well within the limits of technical error. Now I am far from saying that the correspondence is always so clear, but it is necessary to emphasize the fact that there is never a wide divergence, and that

[9] For the opportunity to examine whom, I am indebted to Mr. Wilfred Trotter.

[10] I give the measurements in this form because the time marker is in $\frac{1}{5}$ sec. The figure above the line gives the number of fifths.

[11] It is also due in part to the fact that the electric effect slightly precedes the actual contraction.

as a result of the comparison in a number of cases, it may be affirmed that where the *a*–*c* interval exceeds $\frac{1}{5}$ sec., the P–R interval will be found to have increased, and speaking of practical measurements, the prolongation is of approximately equal extent in both. There can be no question from Fig. 11 not only that the auriculo-ventriculo-systolic interval may be prolonged, but that in certain instances the auricular systole ends long before the ventricular systole starts.

We go back to the earlier but more complex curves. Figs. 12 and 13 are from the same case, but the grade of block is higher. There are dropped beats and the P summits are often falling during the limits of preceding ventricular systoles. The positions of these coincidental beats are marked by dotting the outlines of the T variations in white beneath the composite curves. Where P and T fall together, the former is found by subtracting the known outline of T from the whole summated curve. The events portrayed in Fig. 12 may be compared with those of Figs. 9 and 10, for they are exactly parallel. The phenomena are represented as follows :—

P–R interval $\frac{1{\cdot}2}{5}$, $\frac{1{\cdot}5}{5}$, $\frac{1{\cdot}8}{5}$, dropped beat.

Again, take Fig. 8 (a polygraphic curve obtained on the same day). It shows events which are parallel to those of Fig. 6, the criticized curve. Beats are dropped after each second or each third response ; and there is a widening of *a*–*c* intervals $\left(\frac{1{\cdot}0}{5}, \frac{1{\cdot}7}{5}, \text{and } \frac{2{\cdot}0}{5}\right)$ up to the dropped beat. Note also the rise in the height of *a* as it falls back further and further towards the preceding *c*.

In Fig. 13 I publish another curve taken from this patient on the same day, simultaneous electro-cardiographic and polygraphic tracings, which should lay all doubts of interpretation at rest. The strip may be compared with that part of Fig. 8 in which the intervals are marked. In Fig. 13 each R summit is followed by a *c* wave in the venous curve, while each P summit is succeeded by a wave marked *a* (the separation of *a* and P or *c* and R is approximately by the usual interval, $\frac{0.6}{5}$ sec.). Now in Figs. 7 and 11 the *a* waves are small, and for the reason that auricular and ventricular systoles (*a* and *v* or P and T) do not coincide, while in Fig. 13 the characteristic staircase of *a*'s (a^1 to a^4) is shown as each successive *a* falls further back towards the preceding *c*. The practical interpretation of the curves as a whole is complete ; they are proof against the greatest scepticism. But, says Dr. Brockbank (p. 354), in referring to Fig. 5 :—

'there is a distinct wave at the proper time for that due to auricular systole and following, by as much as 0·30 sec. in some beats, the wave attributed in the tracing to auricular systole.'

I draw Dr. Brockbank's attention to the similar waves in Figs. 8 and 13, waves marked with asterisks, and ask him if by any effort of imagination he can attribute them to an event synchronous with the onset of auricular systole. They fall approximately 0·26 sec. later than the wave marked *a* in this instance. To what are they due? I leave Dr. Brockbank to decide: they are

of little consequence to those of us who look to a practical issue of our observations, for we know from the simultaneous electric curves that the *a* waves marked are due to auricular systoles.

Let me sum up the position. Dr. Brockbank has thought fit to criticize certain published curves. His criticisms are totally invalid. He has attempted to cast doubts upon the interpretation of certain events and certain deductions made from them. The interpretation as originally stated is justified by a careful analysis of the curves themselves, and the conclusions are upheld by an abundance of evidence.

At the present time we are face to face with a mass of new facts, and with problems of considerable complexity. It is not the time for controversy, it is the time for patient endeavour in the collection and sorting of these facts. It is necessary to impress upon my readers that those of us who are intent upon arriving at the meaning of these new facts can ill afford to turn aside from the legitimate path of investigation to reply to criticisms which have no real foundation. And I may be permitted to state once more my emphatic opinion, that if criticism is to be of service, it must come from those who are taking an active part in building up the real knowledge of the subject.

DESCRIPTION OF FIGURES.

PLATE 28, FIGS. 9 and 10. Two electro-cardiograms from separate dogs during periods of asphyxia. P represents auricular and R and T ventricular systole. They show that prolongation of the auriculo-ventriculo-systolic interval occurs in experiment, and that an auricular contraction which originates a ventricular response may fall back upon the preceding ventricular systole.

PLATE 28, FIG. 11; PLATE 29, FIGS. 12 and 13. Electro-cardiographic curves and polygraphic curves from the same case as Figs. 7 and 8. They show in the most conclusive manner that the interpretation of Figs. 7 and 8 is correct; and prove beyond question that clinically auricular and ventricular beats may coincide, where ventricle is responding to auricle, and that prolongation of the auriculo-ventriculo-systolic interval occurs in man. It should be remembered that the curves are but short sections of prolonged tracings. The same series of events was repeated time after time. Time as in all curves is in $\frac{1}{5}$ sec.

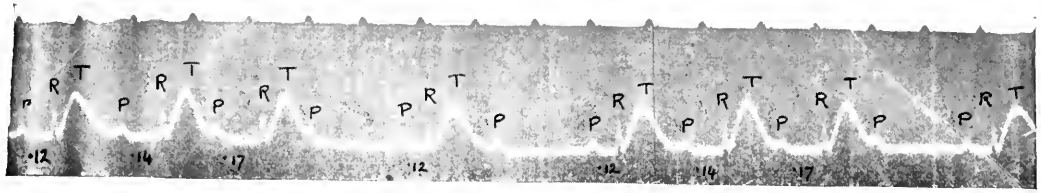


FIG. 9

FIG. 10

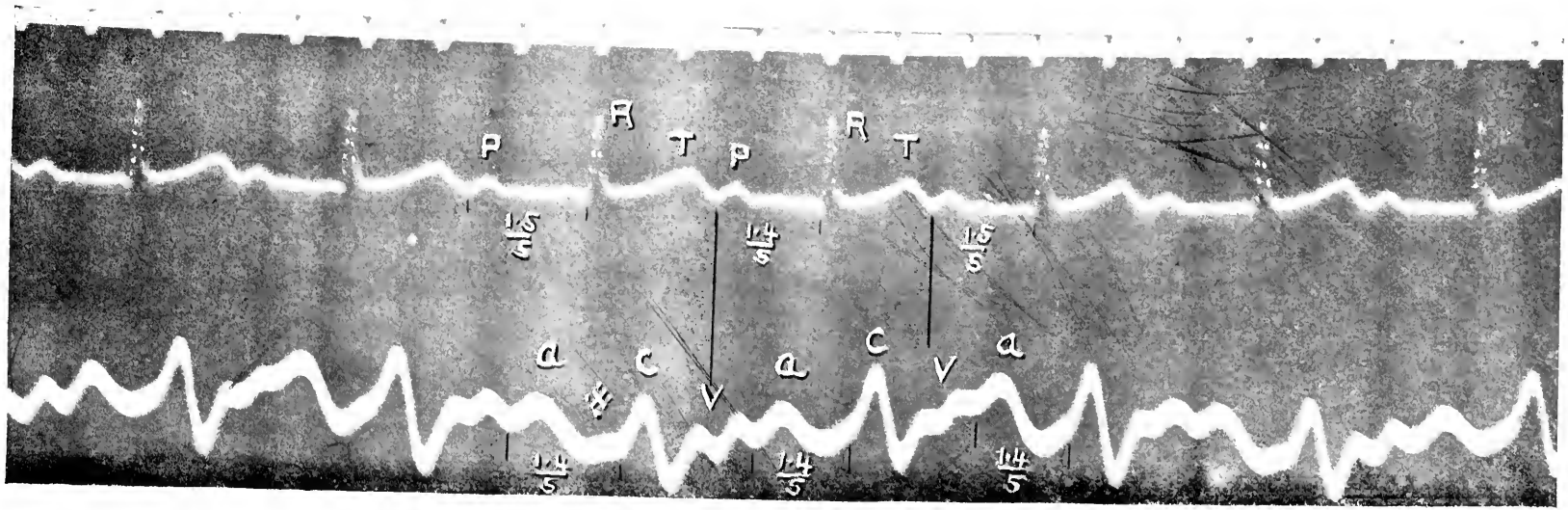


FIG. 11

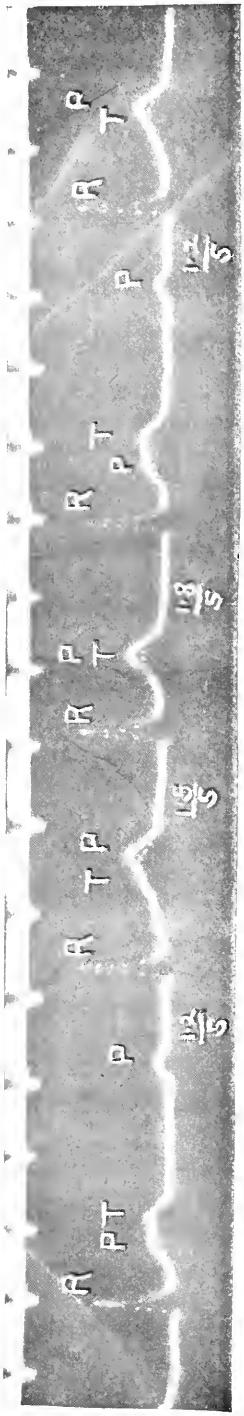


FIG. 12

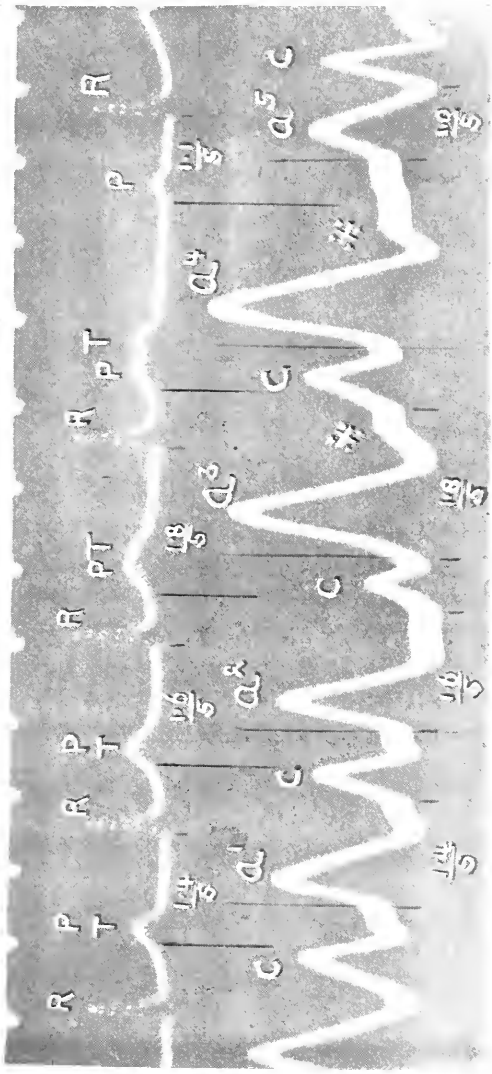


FIG. 13

[*Reprinted from "Heart."*
Vol. II, No. 3, May, 1911.]

CLINICAL OBSERVATIONS ON CONGENITAL HEART DISEASE.*

By R. W. S. WALKER.

(*University College Hospital, London.*)

In investigating congenital heart disease, one is confronted with the difficulty of correlating the physical signs with the lesions found after death. With this in mind, it appeared essential that some attempt should be made to reduce certain of the physical signs to a more orderly grouping. Working on these lines, certain more or less well defined types have been isolated, and they are reported in the following pages. At the same time, suggestions are made as to the relationship of these types to certain anatomical conditions which are well known. In all probability, the diagnosis of rare and complex abnormalities in deep seated organs will always be attended with difficulty; but with the accumulation of detailed and grouped physical signs, finally confirmed by post-mortem records, there seems no reason to suppose that it will not be ultimately possible to make a clinical diagnosis of the predominating underlying lesion in many congenital affections of the heart which are compatible with life. The fourteen cases which follow have been examined solely from the clinical standpoint; an attempt is made to show that they fall into two main groups, the first of which may be again subdivided. The physical signs which characterise each group or subdivision are noted, and a possible explanation of these signs is put forward.

A DESCRIPTION OF FOURTEEN CASES OF CONGENITAL HEART DISEASE.

Group I. Subdivision A.

CASE I. A female, aged 12 years.

Family History. The father died of pulmonary tuberculosis. The mother was healthy.

Past Illnesses. None.

Symptoms. The symptoms had not been prominent, and had been present for two years only; they had consisted of occasional precordial pain, breathlessness on exertion and palpitation. During the six months prior to examination, pulmonary tuberculosis had become evident.

Physical signs. The patient was florid in type. Cyanosis and clubbing of the fingers were absent.

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* Being a portion of a thesis presented and accepted for a doctorate of medicine in the University of Cambridge. The observations were made at the suggestion and under the supervision of Dr. Thomas Lewis.

Cardiac system. The heart's impulse, localized and forcible, was in the 4th space, just internal to the nipple. There was a systolic thrill, faintly perceptible at the apex, which increased in intensity to reach its maximal in the 2nd left space just external to the sternum. It was palpable to the left of the sternum in the whole of the 1st and 2nd spaces in front, and the 3rd space as far as the mid-clavicular line. There was no thrill in the vessels. On percussion* the upper limit of cardiac dulness lay at the 2nd rib, and curved thence to the margins of normal basal dulness. The left limit of cardiac dulness was at the heart's apex beat. The right limit ½ inch external to the sternum. Auscultation at the apex revealed a normal second sound; there was a slight systolic murmur, not conducted outwards, which increased in intensity on being traced upwards. Its position of maximal intensity was in the 2nd space, ½ inch to the left of the sternum. The murmur was harsh in character but not definitely rough. It was audible one inch to the right of the sternum in the 1st and 2nd spaces, in the whole of the 1st and 2nd left interspaces and slightly beyond the mid-clavicular line in the 3rd interspace. It was audible in both carotids and in both interscapular regions behind. The pulmonary second sound was loud, the aortic second sound was accentuated. The pulse was regular and normal. Venous curves showed the *a-c* interval to be of normal length.

Lungs. Signs of pulmonary tuberculosis were present at the left apex and tubercle bacilli were present in the sputum. The other organs were normal.

CASE II. A female, aged 2 years.

Family history. This was traced for three generations; nothing of significance was found.

Past illnesses. None.

Symptoms. This patient came under observation for broncho-pneumonia, prior to which there had been no symptoms.

Physical signs. The patient was florid in type. Cyanosis and clubbing were absent.

Cardiac system. The heart's impulse, rapid and heaving, was in the nipple line of the 5th space. A systolic thrill was present which was similar in character and had a similar distribution to that recorded in *CASE I.* On percussion the upper limit of cardiac dulness lay in the 2nd space; the left limit in the nipple line; the right limit ½ inch to the right of the sternum. On auscultation at the apex, the first sound was normal; the second sound accentuated. A harsh systolic murmur was present, similar in its position of maximal intensity and its area of audibility to that recorded in *CASE I.* It was not audible in the vessels of the neck, nor over the lungs behind. The pulmonary second sound was very loud. The aortic second sound was normal. The remaining systems were normal.

CASE III. A male, aged 7 years.

Family history. There were two other healthy children. The mother was healthy, but one sister had had rheumatic fever, two brothers had had gout. The paternal side was healthy.

Physical signs. Extreme cyanosis was present. Clubbing was not marked. A blood examination showed:—

Red cells	...	10,288,000 per c.mm.
White cells	...	12,000 per c.mm.
Hb. percentage	...	110 per cent.
Colour index	...	·56

Cardiac system. The heart's impulse was in the nipple line of the 5th space. Pulsation was visible in the 4th and 5th spaces. A systolic thrill was present, the limits of which could be accurately mapped out; its palpable area was approximately the same as that noted in *CASES I* and *II.* On percussion the upper limit of cardiac dulness lay in the 2nd space; the left limit ½ inch external to the nipple; the right limit ¾ inch to the right of the sternum. On auscultation the first sound was loud and slapping at the apex. The second sound was barely audible. A systolic murmur, similar in character, distribution and point of maximal intensity to those recorded in the preceding cases, was present. The pulmonary second sound was absent, a short diastolic murmur was heard in this region occasionally. The systolic murmur was not heard in the vessels of the neck, nor in the interscapular region. Pulse 120, rapid but regular. The remaining systems were normal.

* The percussion limits were fixed in all cases with the patient in the supine position.

CASE IV. A male, aged 11 years.

Family history. There was a marked family history of cardiac disease and rheumatic fever. The patient's father died of cardiac disease, two paternal aunts had rheumatic fever and cardiac disease, and one died of cardiac failure. The mother had had rheumatic fever and cardiac disease; a maternal uncle had had rheumatic fever. There was also a cardiac history in the preceding generation.

Physical signs. There was a slight tendency to cyanosis, clubbing was absent. Patient was florid in type.

Cardiac system. The heart's impulse, forcible and heaving, was in the 5th space, just internal to the nipple. A systolic thrill, similar in its area of distribution and in its position of maximal intensity, to that noted in the preceding cases, was present. On percussion the upper limit of cardiac dulness lay in the 2nd space; the right limit ½ inch to the right of the sternum; the left limit in the mid-axillary line. On auscultation the second sound was accentuated at the apex. A blowing systolic murmur, maximal at the apex, was audible over the lower precordium; this murmur was conducted outwards to the axilla. A rough systolic murmur was present at the pulmonary base, its position of maximal intensity and the upper limits of the area of audibility were similar to those noted in the preceding cases. It was barely audible in the 4th space and was absent in the 5th space. The pulmonary second sound was markedly accentuated, the aortic second sound was indistinct. No cardiac murmurs were audible in the vessels of the neck, nor in the interscapular region. The pulse was regular, 80 bears per minute. Venous and sphygmograph curves were taken, the *a-c* interval being of normal length. The remaining systems were normal.

CASE V. A female, aged 8 years.

Family history. The patient's mother and a maternal aunt had had rheumatic fever; and the mother suffered from double aortic and double mitral disease.

Past illnesses. Measles.

Symptoms. This patient had suffered from birth from blueness and breathlessness, which usually succeeded any exertion.

Physical Signs. Cyanosis was present, but clubbing of the digits was absent. The patient was florid in type.

Cardiac system. The heart's impulse was of normal character, and lay at the nipple line in the 4th space. A systolic thrill, similar in every respect to that noted in the preceding cases, was present. On percussion the upper limit of cardiac dulness lay at the 2nd rib, and curved thence to the margins of normal basal dulness. The left limit of cardiac dulness lay ½ inch external to the nipple line; the right limit 1 inch external to the sternum. At the apex auscultation revealed an accentuated second sound. There was a blowing systolic murmur, maximal 1 inch internal to the apex, which was conducted outwards to the axilla. On tracing this murmur towards the base, it became fainter, and at the level of the fourth rib, a harsh grating systolic murmur became audible. This murmur was maximal in the middle of the sternum at the level of the 2nd rib cartilage and was equal in pitch all over the aortic and pulmonary cartilages. It was audible over the whole upper half of the chest, in the vessels of the neck and over the lungs behind, being most marked in the right interscapular region. The pulmonary second sound was accentuated. The pulse was 80, and normal in character. Polygraphic tracings showed the *a-c* interval to be normal in length.

Group I. Subdivision B.

CASE VI. A female, aged 8½ years.

Family history. This was traced for three generations. The mother had severe chorea when three months pregnant with this patient, and presented well marked signs of double mitral disease and pulmonary tuberculosis. In the three generations, nine persons (exclusive of this patient and out of a total of thirty-two) had had rheumatic fever or cardiac disease.

Past illnesses. Measles and "pulmonary congestion."

Symptoms. The patient's symptoms had been blueness, slight breathlessness and pain in the left axilla. The blueness dated from birth; it disappeared at times for long intervals.

Physical signs. Cyanosis and clubbing was absent. Patient florid in type.

Cardiac system. The heart's impulse was in the 4th space, one inch external to the nipple line. A systolic thrill was present, the area of which was readily defined and with accuracy. It was confined to the precordium with the exception of a divergence of 1½ inches to the left in the 2nd and 3rd left intercostal spaces. The region of maximal intensity constituted a zone extending from the left 3rd rib to the 4th space immediately external to the sternum. On percussion the upper limit of cardiac dulness lay in the 2nd space; the left limit at the heart's apex beat; the right limit ½ inch to 1 inch to the right of the sternum. On auscultation, a loud harsh systolic murmur was heard. The area of maximal intensity of this murmur coincided with that of the thrills. At the pulmonary cartilage it was very superficial. This murmur was audible all over the chest in front and over the lungs behind; it was more intense on the left than on the right side. It was not audible in the veins of the neck. The apical second sound was loud and harsh. The pulmonary second sound was loud and slapping. The aortic second sound was weak. The pulse was 120, but otherwise normal in character. Polygraphic tracings were taken, and showed the *a-c* interval to be normal. Well marked signs of pulmonary consolidation were present at the left apex.

CASE VII. A female, aged 6 years.

Family history. Traced for several generations; there was no history of rheumatism, fever or cardiac disease.

Past illnesses. None.

Symptoms. This patient had had no cardiac symptoms, her cardiac symptoms were discovered during the course of a routine examination.

Physical signs. Cyanosis and clubbing were absent. The patient was florid in type.

Cardiac system. The heart's impulse was in the 6th space, ½ inch external to the nipple; pulsation was visible in the 4th, 5th and 6th spaces. A systolic thrill was present, which covered a similar area and had a similar zone of maximal intensity to that found in the preceding case. On percussion the upper limit of cardiac dulness lay at the 3rd rib; the left limit at the heart's apex beat; the right limit ½ inch external to the sternum. On auscultation a systolic murmur was present, similar in character, in its area of audibility in front and behind, and in its zone of maximal intensity to that noted in the preceding case, with the exception that this murmur was audible in the vessels of the neck. The apical second sound was accentuated, while both pulmonary and aortic second sounds were weak. Pulse 80, normal in rhythm and quality. The remaining systems were normal.

Group II.

CASE VIII. A female, aged 3½ years.

Family history. This was traced for three generations. Two cases of rheumatic fever or cardiac lesion occurred. A maternal aunt had rheumatic fever and died of cardiac disease; a maternal uncle died from paralysis, which on investigation of the records of the hospital proved to have been caused by an embolism from mitral stenosis.

Past illnesses. Measles and chicken-pox.

Symptoms. None. She had had "convulsions" at the age of 2½ years and her cardiac condition was discovered during a routine examination at that age.

Physical signs. Cyanosis and clubbing were absent. Patient was pallid and anæmic.

Cardiac system. The heart's impulse was in the 5th space, ½ inch external to the nipple line. On percussion the upper limit of cardiac dulness lay at the 1st rib and curved sharply to the normal dulness at the 3rd rib; the left limit of cardiac dulness lay ¾ inch external to the nipple; the right limit 1 inch to the right of the sternum. On auscultation, the first sound was accentuated and the second sound was slightly exaggerated. There was a slight systolic murmur, which increased in intensity on being traced upwards. In the 4th space, the murmur ran right into the second sound. In the 3rd space the murmur was loud and harsh; it started immediately

after the commencement of the systole and ran into a reduplicated second sound, the last half of which faded away into a short diastolic murmur. The position of maximal intensity was at the pulmonary cartilage, where it was continuous. It was a loud harsh murmur which ran through the accentuated second sound, being somewhat reinforced at this instant, and continued as a diastolic murmur. This murmur was audible over the whole of the 1st and 2nd and 3rd left interspaces in front and in the 4th space to a point ½ inch external to the nipple; while it was audible 1 inch to the right of the sternum in the 1st and 2nd spaces. Its area of audibility and position of maximal intensity corresponded closely with those of the systolic murmur in *CASE I.* In tracing the murmur outwards from the pulmonary cartilage, the diastolic element became correspondingly inaudible. It was audible in the vessels of the neck and over the lungs behind. The aortic second sound was normal. The pulse was 100, closely simulating Corrigan's pulse in type; capillary pulsation was not clearly established.

CASE IX. A female, aged 15½ *years.*

Family history. The family tree was traced for several generations. A maternal sister had had rheumatic fever and a cardiac lesion.

Past illnesses. Measles.

Symptoms. Breathlessness on exertion.

Physical signs. Cyanosis and clubbing were absent. The patient was florid in type.

Cardiac system. The heart's impulse was in the 5th space just internal to the nipple. An early diastolic thrill was present at the apex, which on being traced upwards merged into an almost continuous thrill, maximal at the pulmonary cartilage. This thrill started just after systole commenced and its palpable area was similar to that of the systolic thrill of the preceding case. On percussion the upper limit of cardiac dulness lay in the 1st space; the right limit ½ inch to the right of the sternum; the left limit 1 inch outside the nipple line. On auscultation, the first sound was accentuated at the apex and there was a systolic murmur which was conducted outwards to the axilla. There was a continuous murmur, maximal at the pulmonary base. The area of audibility of this murmur and the conduction character were similar to those of the preceding cases. Only the systolic portion was audible in the vessels of the neck. The aortic second sound was normal. The pulse was 132. Corrigan's pulse and capillary pulsation were present. Polygraphic tracings showed a well marked *pulsus bisferiens*, while the *a-c* interval was normal.

The remaining systems: signs of pulmonary consolidation were present at the left apex.

CASE X. A married woman, aged 38 *years.*

Family history. One child died of rheumatic fever. The family history could not be traced in detail.

Past illnesses. Uncertain. Rheumatic fever, chorea and scarlet fever were definitely denied.

Symptoms. Precordial pain at intervals for a year only.

Physical signs. Cyanosis and clubbing were absent. The patient was pale.

Cardiac system. The heart's impulse beat was in the 6th space, two inches external to the nipple line. A systolic thrill, similar to that recorded in *CASE VIII*, was present. On percussion the upper limit of cardiac dulness lay at the 2nd rib, and curved markedly outwards to the 3rd rib. The left limit of cardiac dulness lay 6½ inches from the mid-sternal line; the right limit 1 inch to the right of the sternum. On auscultation, a loud continuous murmur was present at the pulmonary cartilage. The murmur was similar to that of the preceding cases. It was maximal at the pulmonary cartilage, and on tracing it outwards, the diastolic portion became correspondingly shorter. At the apex the first sound was accentuated. The aortic second sound was also increased. The pulse was regular and somewhat abrupt. Polygraphic tracings showed the *a-c* interval to be normal.

CASE XI. A male, aged 12 years.

Family history. This could not be traced in detail. No history of rheumatism or cardiac disease could be obtained.

Past illnesses. Measles and chicken pox.

Symptoms. None.

Physical signs. Cyanosis and clubbing were absent. The patient was pallid.

Cardiac system. Pulsation marked in the 2nd to the 6th spaces. The heart's impulse was in the 6th space, 1 inch external to the nipple line. There was a well marked systolic thrill, maximal at the pulmonary cartilage. On percussion the upper limit of cardiac dulness lay at the 2nd rib; the right limit 1½ inches to the right of the sternum; the left limit ½ inch external to the heart's apex beat. On auscultation, the first sound at the apex was accentuated and there was an almost continuous murmur increasing with the systole and failing just before the first sound recommenced. The murmur was maximal at the pulmonary cartilage, where it was loud, harsh and continuous. The conduction of the murmur was similar to the type *CASE VIII.* The systolic portion of the murmur at the apex was conducted outwards towards the axilla. The aortic second sound was normal. The pulse was 96, regular but markedly double. Capillary pulsation was visible. Polygraphic tracings showed a well marked *pulsus bisferiens*, while the *a-c* interval was normal.

This patient had an abnormal right carotid artery crossing the trachea and visible in the episternal notch.

CASE XII. A married woman, aged 29 years.

Family history. This was traced for a number of generations. One sister, the father, two paternal relations had had either rheumatic fever or cardiac disease.

Past illnesses. Measles, chicken pox, rheumatic fever.

Symptoms. These were very slight. She had occasionally had slight dyspnœa, she had also suffered from hystero-epileptic fits.

Physical signs. The patient had well marked congenital defects in the lobes of the ear on either side, (Fig. 1); an accessory auricle, hard and cartilaginous was present on the cheek

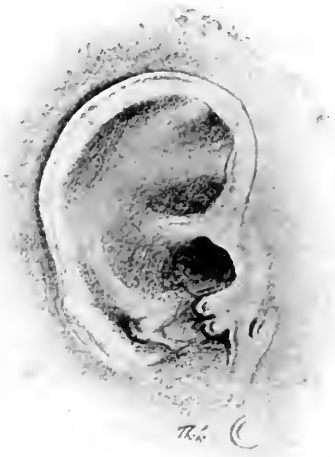


FIG. 1.

midway between the tympanum and the angle of the mouth. There was a congenital dermoid tumour in the conjunctiva at the outer angle of each eye. Cyanosis was absent.

Cardiac system. The heart's impulse was in the 6th space, 6 inches from the sternum. There was a thrill which was maximal at the pulmonary cartilage, which commenced in systole and was continuous. On tracing the thrill outwards the diastolic element became reduced. On percussion the upper limit of cardiac dulness lay in the 2nd space; the left limit 6 inches from the

mid-sternal line; the right limit ½ inch to the right of the sternum. On auscultation, there was a continuous murmur over the whole of the precordium. It was maximal at the pulmonary cartilage. The conduction of the murmur was similar to that in the preceding cases. At the apex the first sound was accentuated. The aortic second sound was normal. The continuous murmur was audible in the vessels of the neck. The pulse was 96; capillary pulsation and Corrigan's pulse were present; polygraphic tracings showed the *a-c* interval to be normal.

CASE XIII. A male, aged 42 years.

Family history. Traced for several generations; no history of rheumatic fever or cardiac disease.

Past illnesses. Measles.

Symptoms. None, his condition being discovered during an attack of appendicitis.

Physical signs. Cardiac system: the heart's impulse was in the 5th space, 4 inches from the middle line. A systolic thrill was present at the pulmonary cartilage. On percussion the upper limit of cardiac dulness lay at the 3rd rib; the left limit at the heart's apex beat; the right limit ½ inch to the right of the sternum. On auscultation there was a soft systolic murmur at the apex, which was conducted outwards to the axilla. The second sound was very weak. There was a continuous murmur at the pulmonary cartilage, the systolic element of which was harsh, the diastolic soft and blowing. Outside this area the murmur was double. The interval between the two parts decreasing towards the pulmonary cartilage. The double murmur was audible in both interscapular regions. The systolic element followed by a clear second sound was alone present in the vessels of the neck. The pulse was 88 normal in rhythm and character. Polygraphic tracings showed the *a-c* interval to be normal.

CASE XIV. A male, aged 20 years.

Family history. Traced for several generations; no history of rheumatic fever or cardiac disease.

Past illnesses. Measles.

Symptoms. Slight precordial pain for three months only before examination.

Physical signs. Cyanosis and clubbing were absent.

Cardiac system. The heart's impulse was in the 5th space, 3½ inches from the mid-sternal line. There was a continuous thrill at the pulmonary cartilage, the systolic element of which was alone palpable and over the usual area. On percussion the upper limit of cardiac dulness lay at the 3rd rib; the left limit at the heart's apex beat; the right limit 1½ inch to the right of the sternum. On auscultation both sounds were accentuated at the apex. There was a continuous murmur at the pulmonary cartilage and it was similar in character and had a corresponding conduction to that of the preceding cases. The aortic second sound was normal. The pulse was 80, and distinctly of the Corrigan type. Capillary pulsation was present; polygraphic tracings showed the *a-c* interval to be normal.

A CLINICAL SUBDIVISION OF CONGENITAL PULMONARY STENOSIS.

Group I. (CASES I-VII, in which the main physical sign was a harsh murmur confined to systole, and maximal in the pulmonary area.)

The past and present symptoms of these patients pointed to cardiac disease. Dyspnoea, precordial pain, palpitation and cyanosis, varying from time to time, were the chief symptoms and they frequently dated from birth. In no case were the symptoms referable to an acute illness. The facial aspect of the cases in this group was uniform, high colouring in the lips, cheeks, and mucous membranes was always present. Cyanosis was observed in three cases only (*III, IV* and *V*). Every case showed right-sided enlargement of the heart, though this was more marked in some than others. A systolic thrill was present in all, and in each of these cases it was of maximal intensity at or near the pulmonary cartilage. A rough and loud systolic murmur, also maximal at this point, accompanied the thrill. But while the signs agreed in their main characteristics with a stenosis of a vessel in the neighbourhood of the pulmonary cartilage, so many points of difference were

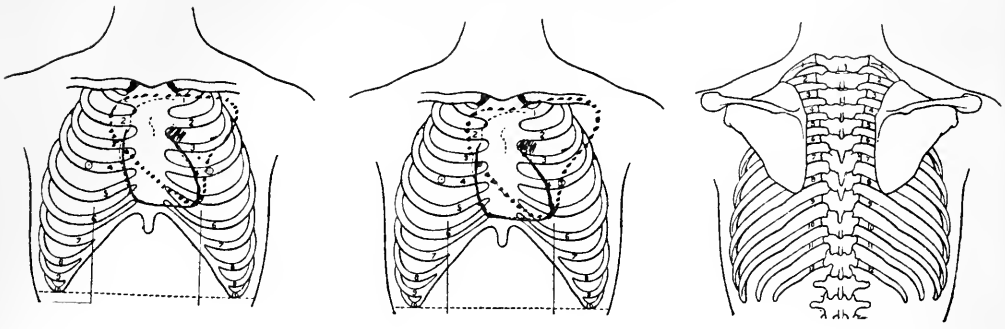
presented by *CASES VI* and *VII*, that it has seemed possible to effect the following sub-division :—

Sub-group A. (*CASES I- V*) in which all the physical signs were found relatively high in the chest.

Sub-group B. (*CASES VI* and *VII*) in which the physical signs were relatively low in the chest.

Sub-group A. (*CASES I- V*) In these five cases the position of maximal intensity of the systolic thrill (Fig. 2*a* shaded area) was situated at the pulmonary cartilage and was localized at this spot. The thrill was palpable over a relatively large area of the chest. As will be seen from the upper line of the diagram (Fig. 2*a* dotted line), this area comprised the upper precordium, the left infra-clavicular region as far outward as the line of the anterior axillary fold, and a small region to the right of the sternum in the 1st and 2nd spaces. On auscultation a rough systolic murmur accompanied the thrill. The position of maximum audibility of this murmur was localized at the pulmonary cartilage (Fig. 2*b*, shaded area), and the area of audibility of this murmur in front was approximately that of the palpable area of the thrill (Fig. 2*b*, dotted line). In two cases, *I* and *V*, the murmur was audible in the vessels of the neck, and over the lungs behind, more especially in the left and right interscapular regions. With these exceptions the murmur was not heard in the above mentioned positions, the cardiac first sound being clear. The pulmonary second sound was inaudible in *CASE III* ; in the remainder it was accentuated, sometimes to a very marked degree. In two cases, *I V* and *V*, there was an apical systolic murmur, conducted well outwards ; with these exceptions the cardiac sounds were normal.

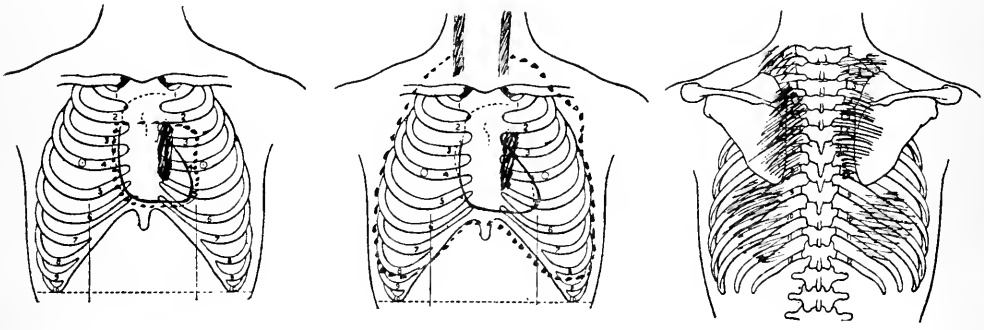
Sub-group B. (*CASES VI* and *VII*) In these two cases the area of maximal intensity of the systolic thrill was larger than that occurring in the cases of the preceding sub-division, and extended downwards in a narrow zone along the left border of the sternum (Fig. 3*a*, shaded area), from the pulmonary cartilage to the 4th and 5th interspaces. The area over which the thrill was palpable was limited in extent, it included the whole precordium, and a small region in the 2nd and 3rd left interspaces, external to the precordium (Fig. 3*a*, dotted line). A rough systolic murmur accompanied this thrill, the area of maximal intensity of which coincided with that of the thrill (Fig. 3*b*, shaded area). This murmur, which was very superficial at the pulmonary and 3rd cartilage, was audible over the whole of the chest in front and over the lungs behind, more especially in the left interscapular region (Fig. 3*b*, dotted outline, and 3*c*, shaded area). The pulmonary second sound was markedly accentuated in *CASE VI* and was diminished in *CASE VII*. The only other difference noted in the physical signs of these two cases was that in the latter, the murmur was audible in the vessels of the neck.



a. *b.* *c.*

Fig. 2. *Group I. A.*

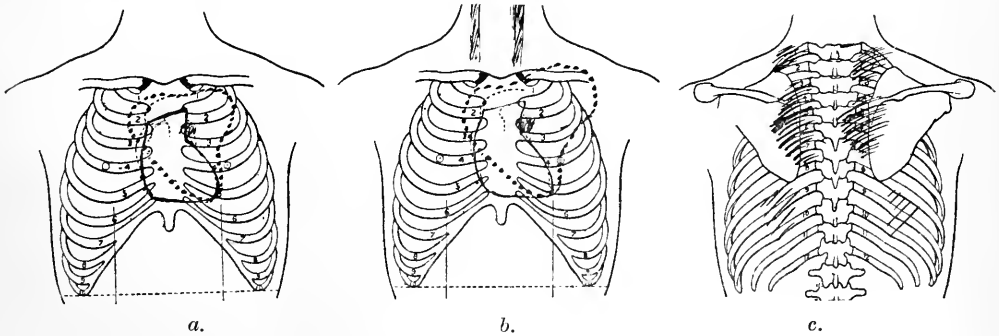
a. The Thrill. Area of maximal intensity shaded, area of palpability dotted.
b. The Murmur. Area of maximal intensity shaded, area of audibility dotted.
c. Murmur not audible behind.



a. *b.* *c.*

Fig. 3. *Group I. B.*

a. The Thrill. Area of maximal intensity shaded, area of palpability dotted.
b. The Murmur. Area of maximal intensity shaded, area of audibility dotted.
c. Murmur audible behind over shaded area.



a. *b.* *c.*

Fig. 4. *Group II.*

a. The Thrill. Area of maximal intensity shaded, area of palpability dotted.
b. The Murmur. Area of maximal intensity shaded, area of audibility dotted.
c. Murmur audible over shaded area behind.

The points of difference between Sub-group *A* and *B* of Group *I* are as follows :—In group *I*, *A* the area of maximal intensity of the thrill was localized at the pulmonary cartilage, in group *I*, *B* it extended downwards from this point along the left of the sternum to the 4th interspace. In group *I*, *A* the thrill was palpable over the upper half of the left chest in front, in group *I*, *B* it was not felt above the precordium, and extended lower, so as to include the whole precordium. The area of maximal intensity of the systolic murmur coincided in each case with that of the thrill. In group *I*, *A* the audibility of the murmur was limited to the left upper half of the chest in front, in group *I*, *B* the murmur was heard all over the chest in front and behind and in one case in the vessels of the neck.

Group II. (*CASES VIII-XIV, in which the main physical sign was a harsh murmur commencing in systole, continuing into diastole, and maximal in the pulmonary area*).

The symptoms in this group were often so slight that the condition was discovered only on routine examination. This occurred in *CASES VIII*, *X*, *XIII* and *XIV*. In the remainder the symptoms were not severe, dyspnoea on exertion being the most constant. The facies were distinctive, the features being pallid and the lips and mucous membranes anæmic. Cyanosis, or a history of it was absent throughout. On palpitation, a thrill was detected, which in three cases, *IX*, *XII* and *XIV*, could be definitely ascertained as continuing into diastole ; in the remainder the thrill was systolic only. The position of maximal intensity of the thrill was localized at the pulmonary cartilage (Fig. 4*a*, shaded area), and the area of palpability included the upper precordium, a small space to the right of the sternum in the 1st and 2nd interspaces, and the left upper half of the chest below the clavicle (Fig. 4*a*, dotted line). The area of this thrill coincided approximately with that noted in group *I*, *A*. On percussion the right limit of cardiac dulness was enlarged. A marked feature of this group, only absent in two cases (*XIII* and *XIV*.) was a zonular upward enlargement of the basal cardiac dulness over and slightly to the left of the sternum. This enlargement extended sometimes to the first interspace ; it was present, but not to such a marked degree in two cases of group *I* (*I* and *V*). The characteristic physical sign of this group was the additional murmur. A continuous murmur in the pulmonary area was present in every case. It started as a harsh bruit in systole, was reinforced at the commencement of diastole, and becoming softer and less audible, tailed away in diastole, to start again at systole. The position of maximal intensity of the murmur was at the pulmonary cartilage (Fig. 4*b*, shaded area), traced from this point the diastolic element became less audible, so that at the limits of the area of audibility the systolic element was alone heard. The area of audibility of this murmur was fairly constant (Fig. 4*b*, dotted line and 4*c*, shaded area). It included the upper half of the left chest and a small region in the 1st and 2nd right interspaces and was very similar to that noted in group *I*, *A*,

save that there was a greater tendency for the left supraclavicular and axillary regions to be included. Either as a systolic or as a continuous sound it was audible in the vessels of the neck and over the chest behind, more especially in the left interscapular region. The second pulmonary sound was present at the pulmonary cartilage, it was frequently accentuated and occasionally reduplicated. The second sound at the aortic cartilage was normal with one exception. In three cases, *IX*, *X* and *XIII*, there was an apical murmur conducted outwards to the axilla.

The pulse, with the exception of *CASE XIII*, tended to rise and fall abruptly and in four cases (*IX*, *XI*, *XII* and *XIV*) this was so well marked as to constitute a well marked water-hammer pulse. In the four cases mentioned, capillary pulsation was present. In *CASES XI* and *XIV*, the murmur was increased in intensity by deep inspiration.

The physical signs which group I and II possess in common; and those which are distinctive of one or other group.

Though the cases comprising group *II* are clearly separable clinically from those of group *I*, certain physical signs are common to both; while the distinguishing physical signs may be looked upon as additions to those presented by the cases of group *I*. Right sided enlargement of the heart was common to both groups. In all save three cases (*IX*, *XII* and *XIV*) of group *II*, a systolic thrill was present at the pulmonary cartilage. The thrill was very similar both in its position of maximal intensity and in its area of palpability to that observed in group *I*, *A*. In three cases (*IX*, *XII* and *XIV*) the thrill commenced in systole and was continued into diastole at the position of maximal intensity. It was the systolic element of this thrill which was widely conducted over the same area as in the preceding cases.

The main distinguishing features of group *II* as opposed to group *I* were as follows:—

(1). *The notable differences in the history, symptomatology and mode of life.* As has been noted, symptoms in the patients in group *II* were inconspicuous or absent. In the majority of cases, the cardiac malformation in no way precluded the patient from leading an active life; whereas dyspnoea, sometimes severe in grade, was characteristic of the patients in group *I*. The average age of the patients in group *I* was considerably less than that of those in group *II*, the average being 8 years and 23 years respectively.

(2). *The area, character and duration of the murmur.* The murmur, like that occurring in the cases of group *I* was maximal at the pulmonary cartilage. Though commencing as a harsh bruit in systole, it was prolonged as a softer murmur throughout diastole and was continuous. The conduction, either as a systolic or as a prolonged murmur, into the vessels of the neck and

into a wide area behind was constant. The conduction of this murmur in front and its points of resemblance with the murmur in group *I* have been noted in a preceding paragraph.

(3). *The character of the pulse.* The tendency towards the occurrence of Corrigan's pulse and capillary pulsation was a marked feature in group *II*. These signs occurred in no case of group *I*.

(4.) *The increased dulness at the base of the heart.* An increase in the basal cardiac dulness, while occuring in group *I*, notably *CASE V*, was a constant feature in group *II*. This dulness extended upwards in a narrow zone, (Fig. 4 *a*) to the level of the first intercostal space. The presence of this abnormal zone of dulness may conceivably be connected with the audibility of the murmur behind.

A table comparing the symptoms and physical signs of Groups I and II.

	Group I.	Group II.
Symptoms.	Relatively pronounced.	Relatively slight.
Facies.	Florid, often cyanosed.	Pallid and anaemic.
Right sided cardiac enlargement.	Present.	Present.
Dulness over the sternum.	Infrequent (present in *CASES I* and *V*.	Frequent and pronounced.
Maximal intensity of thrill.	Pulmonary cartilage (systolic)	Pulmonary cartilage (continuous).
Area of palpability.	Group *I*, *A*. Upper precordium, left infra clavicular region to anterior axillary fold.	The same (systolic).
Maximal intensity of murmur.	Pulmonary cartilage.	The same (systolic).
Area of audibility of systolic portion of murmur.	Group *I*, *A*. Upper precordium, left infra clavicular region to anterior axillary fold.	The same.
Audibility of murmur in vessels of neck.	Group *I A*: *CASES I* and *IV* Group *I*, *B*: *CASE VII*.	Constantly audible.
Audibility behind.	Group *I*, *A*: *CASES I* and *VI* Group *I*, *B*: *CASES VI* and *VII*.	Constantly present.
Corrigan's pulse and capillary pulsation.	Absent throughout.	Frequently present.

GENERAL DISCUSSION OF THE POSSIBLE MEANING OF THE PHYSICAL SIGNS.

Group I, A and B. The cases in group *I, A* follow the established description of stenosis of the pulmonary valve with sufficient accuracy to allow such a diagnosis to be made.

From the recognised signs of pulmonary stenosis, the cases comprising group *I, B* are somewhat divergent. Yet there are many features held in common with group *I, A*. The history of the symptoms, the facies and the occurrence of cyanosis may be mentioned. The thrill, systolic in time, was maximal at the pulmonary cartilage, but the area of maximal intensity extended downward to the left of the sternum ; while the thrill was palpable only over the precordium. The maximal intensity of the murmur coincided with that of the thrill, but the murmur was audible over the whole chest in front and behind. From a consideration of the points in common between groups *I, A* and *B*, from the situation and area of the zone of maximal intensity of the thrill and murmur, it seems reasonable to suppose that the point of stenosis in group *I, B* is situated, not at the pulmonary valves, but in the infundibulum of the right ventricle. This seems a reasonable explanation of the somewhat large area of maximal intensity of the murmur and thrill in this subdivision, and of the extension of this murmur to, and its superficiality at, the pulmonary cartilage. Anatomical findings make it difficult to conceive that the physical signs of the condition, commonly termed pulmonary stenosis are constant. Greil [3] working at the development of mammalian heart, and Keith[4] working upon malformed human heart, have each brought forward the view that embryologically there is a fourth chamber to the heart. Keith says of this : " The fourth part is the *bulbus cordis*, so well seen in the shark's heart. It is usually supposed that the *bulbus cordis* has disappeared from the mammalian heart, but we have good reason for believing that the bulbus cordis has become included in the right ventricle, forming that part loosely termed its infundibulum. A large number of the very commonest malformations of the human heart are due to an arrest of the process which ends in the incorporation of the bulbus cordis in the right ventricle. The great majority of cases of congenital stenosis of the pulmonary artery are of this nature." Taking a series of 130 cases of so-called pulmonary stenosis, he effects no fewer than five subdivisions on anatomical grounds. In the 19 cases of his first subdivision, the infundibulum is very large, and the point of stenosis is situated comparatively low in the right ventricle. In the remainder the stenosis is much higher in position, and this alteration of site is regarded by Keith as one of the evidences of absence of, or incomplete expansion of the fourth chamber (the infundibulum). It may be noted that this condition occurred in 14·6 per cent. of Keith's cases of pulmonary stenosis. The incidence in the present collection, assuming the diagnosis to be correct, is 14·3 per cent.

Group II. In the general account of group *II*, it has been shown that these cases were characterised by the same features as those of group *I* up to a certain point, with additions to the physical signs. The added phenomena were the freedom from symptoms, the diastolic portion of the murmur, Corrigan's pulse, capillary pulsation and a constant area of well marked dulness over the manubrium. The continuous murmur was described by Gibson[2] and clearly shown by him to be the result of patency of the ductus arteriosus. Libman[6] and Bommer[1] have also described the murmur as an accompaniment of the same lesion.

The patients in group *II* presented few signs of circulatory disturbance, their symptoms were as a rule slight or altogether absent, and their average age was much greater than that of group *I*. Assuming the presence of pulmonary stenosis, persistency of the ductus arteriosus may be regarded as advantageous to the circulation. When a severe grade of stenosis is present, deficient aeration may be expected, and it is obvious that the patency of the ductus arteriosus will to a great extent overcome and eliminate this difficulty, for pulmonary stenosis is usually associated, as we know, with a patent interventricular septum.

Turning to the anatomical data it is found that patency of the ductus Botali, unaccompanied by any other lesion, is rare. Keith[4] mentions that he has found it twice, presumably in his series of 270 cases. The very high proportion of cases presenting continuous murmurs, in this collection of cases (7 out of 14) at once negatives the conclusion that the only lesion was a patent ductus. The frequent combination, pulmonary stenosis and patent ductus arteriosus is emphasised by Peacock,[7] and the collected anatomical observations of these and other writers harmonises with the view adopted, namely the presence of the double lesion in group *II*.

The occurrence of a water-hammer pulse and capillary pulsation in patent ductus arteriosus cases.

Reference has been made to the occurrence of the above phenomena in group *II*. In the sphygmographic tracings of this group the radial upstroke is abrupt. In these cases, notably, in *CASES IX*, *XI*, *XII* and *XIV*, a water-hammer pulse was present on raising the arm, and capillary pulsation was noted. These physical signs, commonly characteristic of aortic regurgitation, are by no means incompatible with the mechanics of the circulation in a case of patent ductus arteriosus; for while in a disease of the aortic valves, there is regurgitation into the ventricle, in patency of the ductus, there is a reflux into the pulmonary artery. As in aortic regurgitation, so in this last condition, the regurgitating blood will be greater in some cases than in others, and this phenomenon may be expected, and judging from the signs is actually found, to show varying grades of prominence from case to case and with different phases of respiration.

The incidence of rheumatic fever and cardiac disease in the family history.

In *CASE I* no reliable details of the family history could be obtained. In nine cases detailed family trees (for three generations wherever possible) were compiled, while in the remainder (*III*, *V*, *X* and *XI*) the family history was traced as fully as the circumstances allowed. Excluding *CASE I*, five cases (*II*, *VII*, *XI*, *XIII* and *XIV*) showed no tendency for the individual or the family to be infected with rheumatic fever, chorea or cardiac valve lesions. In the remaining eight cases, the occurrence of rheumatic fever and cardiac affections was a feature in the history of the family, and sometimes a very marked one.

CONCLUSIONS.

(1) By a careful examination of the physical signs in patients suffering from congenital morbus cordis, it is probable that, with the accumulation of details, such cases will be divided into clinical groups of distinctive types, and that eventually, when such clinical groups have been established and the morbid conditions associated with them described, the diagnosis of one lesion from the other, and the prognosis based upon it, will be possible.

(2) Exclusive of other lesions, such as septal defects, there appear to be at least three clinical groups of pulmonary stenosis :—

I, *A*. Cases in which the signs seem to indicate a constriction in the neighbourhood of the pulmonary valves. High stenosis.

II, *B*. Cases in which the signs seem to indicate a constriction and incomplete fusion of the infundibulum with the body of the right ventricle. Low stenosis.

II. Cases in which there are evidences that the ductus arteriosus is also patent.

(3) Patent ductus arteriosus may give rise to a water-hammer pulse and capillary pulsation.

(4) In many cases of congenital heart disease, and more especially when there is evidence of ductus arteriosus patency, an abnormal zone of basal cardiac dulness is present.

(5) There seems to be evidence that where pulmonary stenosis is accompanied by patency of the ductus arteriosus the symptomatology is less severe and life more prolonged.

(6) A large percentage of cases of congenital heart disease, associated with pulmonary stenosis, give a definite history or family history of rheumatic infection, or a history of cardiac disease in other members of the family.

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REPORT OF A CASE OF TRANSIENT ATTACKS OF HEART-BLOCK, INCLUDING A POST-MORTEM EXAMINATION.

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1. *Clinical Record.*

The facts in regard to this case have been obtained through the kindness of Dr. H. Bazett of Hendon, to whom we are indebted for many observations upon the patient.

The patient was an old maiden lady of eighty, in poor circumstances. There was a history of rheumatic fever, from which she had suffered on two occasions, at the ages of 3 and 40 respectively. At the age of 56, she had three fits of an indefinite nature, otherwise her health had been good. She had lived a very active life, and even in old age was exceptionally energetic. There was a history of ulceration of the legs, preceding the latest attacks of giddiness. She used to suffer frequently from bilious attacks, during which she was occasionally affected by slight jaundice.

She was in fair health for many years until March, 1908, when following an attack of "influenza," fits stated to have been of a similar nature to those previously reported, recurred. She suffered from them daily for five weeks, as a rule there were four or five fits a day, the longest fits were of five minutes' duration. In October of the same year, she had a return of the attacks, and they were very numerous, at times amounting to as many as ten per day. There was a respite of two weeks, until three days before she was first seen, by one of the writers when the fits were again present. She was seen by Dr. Bazett during the last two series of attacks (October and November, 1908), and

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the pulse was frequently found to be slow directly after the occurrence of the attacks (27-29 beats per minute). On both occasions there was marked dilatation of the heart directly after the fits.

I examined her on the 14th November, 1908, shortly after the subsidence of an attack, the pulse was found to be irregular at an average rate of about 55. The old lady was sitting up and seemed in a good state of preservation for her years. There were some chronic joint changes and a slight tremor of the hands. Cyanosis and other signs of cardiac failure were absent. The urine was normal.

The limit of the heart's dulness to the right was 1½ inches from the mid-sternal line; the left limit of dulness about 4 inches from the same line. The heart's apex beat was in the fifth space and forcible. There was a loud systolic murmur at the apex; the first and second sounds were clear. The heart's sounds corresponded exactly to the pulse tracings. There was no evidence of premature contractions. Pulsation in the neck was rapid. The tracings showed occasional dropped beats, beats dropped every third cycle and every alternate cycle. The *a-c* interval was of normal length in all the curves. On the 15th, curves were taken and occasional missed beats were found.

On questioning the patent in more detail as to her symptomatology, she stated that she was warned of the onset of the fits by a disturbance of vision, and frequently by a feeling of faintness; that there was no precordial pain, but that when the pulse was slow, she was conscious of her heart beating. The friend who was nursing her stated that during the attacks, she became pale and subsequently blue, and that not infrequently there was twitching of the hands.

On November 18th, Dr. Bazett wrote: "I saw the patient yesterday, she had had several fits in the interval, but the pulse rate had not, I was told, been much affected. While I was there, the pulse rate was at first regular and normal, but missed three single beats in about five minutes. Suddenly she said she felt giddy, as if an attack was coming on, though I felt no change in her pulse, and while she was moving to lie down, four consecutive beats were missed, then everything went normally again and the feeling passed off. The heart was more dilated."

On November 21st, Dr. Bazett wrote: "The patient is well and the pulse normal." On the 22nd November, the pulse was irregular and various grades of partial heart block were present. As a rule 2 : 1 or 3 : 1 heart block was found, at other times, mixed periods of 1 : 1 and 2 : 1 ratios were present. Curves taken at this visit are shown in Fig. 1 and 2.

On December 11th the pulse was reported by the friend to have been at a rate of 27 beats per minute. Dr. Bazett wrote: "I went two or three hours after, when it was 42 and regular. Yesterday it had reached 50, to-day it is 60." There had been an interval of two weeks without attacks, and during the third week, there were only one or two very slight attacks. On the 17th December, Dr. Bazett wrote: "Three days ago the pulse

was 42 and regular, the day before yesterday it was 36 and most irregular. No fits or attacks of giddiness occurred. The patient was up and doing her work in her room. In the afternoon it was slow and later it quickened to normal." And again: "The nearest approach to a fit which I have seen is on one occasion upon which when counting the pulse and finding it normal, she said suddenly: 'I feel giddy, I feel as if an attack is coming on.' Still I felt no change in the pulse. I began to move her to a couch, and while doing so, three successive beats intermitted once, then the pulse became normal, and there was no fit."

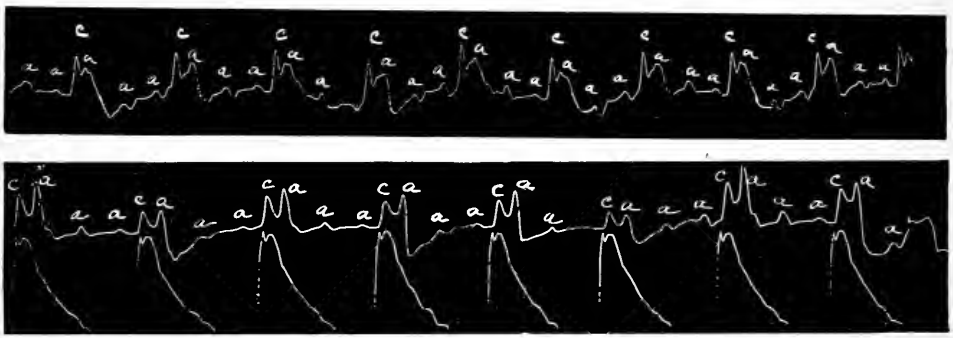

FIG. 1 and 2.

On December 21st, Dr. Bazett wrote that there had been more fits and that the pulse was slow again. She had apparently had fits during the night, and in the morning, the pulse was regular, between 27 and 30 beats per minute. The friend examined her pulse during an attack and found it at the commencement very slow and irregular, but while the fit continued, it became faster. On December 22nd, 2 : 1 heart-block and occasional periods of 3 :1 heart-block were recorded.

On August 29th, 1909, Dr. Bazett wrote to inform me that the patient was dying. She was said to have had many fits since the last report, of a similar nature to those already recounted. The pulse was generally very slow during the fits.

On August 28th, she fell heavily and struck her head. She became unconscious and her condition was critical. I saw her in the evening of the 29th. She was comatose, the limbs flaccid and the breathing stertorous, the temperature had been 101-104. She was obviously moribund and no curves could be taken. The pulse tension was high, there was a tendency to dicrotism, the rate was about 90 beats per minute. Pulsation in the veins of the neck was very distinct and apparently of a perfectly normal form. Two small fluttering movements could be seen with each beat of the pulse, one of which appeared to be presystolic in time.

There had been numerous fits about a fortnight before the accident, and in one of these Dr. Bazett felt the pulse stop for at least one minute.

The patient died on the morning of the 30th August, 1909.

The repeated observations showed that the mechanism of the heart was usually normal, heart block in its several grades was only present at or about the times when fits occurred. *Th. L.*

II. *An account of the Post-Mortem Examination with Special Reference to the Heart.*

The autopsy took place on August 31st, 1909, twenty-four hours after death. The body was that of a moderately nourished woman.

The left temporal muscles and fasciæ showed hæmmorrhages, and they were oedematous. The brain showed sclerosis of the pial vessels of the cortex, but the basal vessels were healthy. Over the right parietal region there was considerable oedema ; the pial membrane was not thickened. In the middle of this area, corresponding to the leg and trunk centres, there was a moderate amount of recent hæmorrhage. There was no hæmorrhage into the ventricles ; the rest of the brain was without change. There were adhesion at both pulmonary *apices*, especially the left ; the *lungs* themselves were voluminous, showed slight oedema and thickening and puckering of the pleuræ at the apices. The *liver* was normal in size, showed moderate stasis with fatty degeneration of the centres of the lobules ; there was no cirrhosis. The *spleen* was small and showed some anthracosis. On the surface were two old infarcts measuring 2·3 centimetres in diameter and extending inward about 2 millimetres. They were of a yellowish-white colour and dense in their consistency. The *kidneys* were small, the capsules somewhat adherent. The vessels were prominent. There were no infarcts. The *gastro-intestinal tract*, the pancreas, and the genito-urinary apparatus were not examined. The right suprarenal capsule had already undergone softening ; the left one was not examined.

The *heart* was enlarged ; the length of the ventricles was 9 cm. ; there was an excessive deposit of fat upon them. The right auricle was dilated, the endocardium whitened ; there was a small Chiari net over the opening of the coronary sinus. The right ventricle was neither dilated nor hypertrophied ; the tricuspid valve was slightly thickened. On the posterior flap of the pulmonary valve, a cauliflower-like vegetation, 5 mm. in diameter. was found This had not the appearance of a recent lesion. The left auricle was dilated, but not hypertrophied ; the endocardium was much thickened. The outflow tract of the left ventricle was dilated and the trabeculæ flattened. The papillary muscles were not hypertrophied, neither was the wall of the ventricle. There was slight retraction (inrolling) of the posterior flap, but both the flaps were thickened above the free edge; the aortic flap of the mitral valve showed marked thickening there was no stenosis. Except for slight thickening and fringe-like vegetations the corpora Arantii, which were themselves slightly thickened, on

the aortic valve was without change. The coronary arteries showed slight atheroma. There was athero-sclerosis of the aorta. The subendo cardial tissue was fatty, showing irregular yellowish streaks throughout, especially in the outflow tract, in the posterior papillary muscle, and in the free trabeculæ. Passing over from the aortic flap of the mitral valve to the lower portion of the pars membranacea septi in a horizontal direction was a strand of dense connective tissue. It will be understood that this structure passed close to the normal site of transit of the *A - V* bundle through the septum.

Microscopic examination of the heart. The heart was fixed in Formol-Müller solution for 36 hours and was then washed in running tap water until clean. It was kept in 70 per cent. alcohol. The usual portion of the inter-auricular and inter-ventricular septum was excised ; that is to say, the part included between an incision which runs parallel to the free edges of the aortic cusps, and backward to the posterior edge of the whole septum, and another parallel with this about 2 cm. below the septum membranaceum and of similar extent. These parallel and horizontal incisions were then joined at their anterior and posterior extremities by vertical ones. The septum membranaceum, the two cusps of the aortic valve (anterior and right posterior), the inter-auricular septum and the posterior wall and surface of the right and left auricles were therefore included in the excised piece. Contrary to the method used in a heart previously reported,[2] the tissue was embedded in its entirety. It was first permitted to lie in thin celloidin for about two weeks, dried rapidly in the air, no excess of celloidin being allowed to remain on the surface, cleared in cedar wood oil, and finally embedded in chloroform and paraffin. The ease in cutting was greatly facilitated by using the vacuum device recommended by W. Henwood Harvey.[3] Forty minutes sufficed for the thorough impregnation of this rather large piece of tissue. The block was cut in serial sections, 10 micra thick, and every fifth section mounted. The entire series was stained with Weigert's iron-hæmatoxylin and Van Gieson's solution.

The sclerosis seen at the post-mortem was again demonstrated microscopically, both in the aorta and in the cusps of the aortic valve. While here and there small areas of round cell infiltration appeared, the entire process might be described as one of replacement sclerosis. The lesion did not appear to be syphilitic. A general increase in the connective tissue was also seen in the small vessels in the posterior portion of the inter-auricular septum, where the adventitia was markedly thickened. There was no endarteritis ; the lumina of the vessels was not contracted. The periarteritis also involved the aorta to a slight extent. The nerve bundles and the ganglia which were found in the inter-auricular septum showed an increase in the connective tissue of the neurilemma and of the endonerium.

There were numerous places in the wall of the right auricle, rather close under the endocardium, where a marked increase in the interstitial connective tissue, with corresponding atrophy of the subjacent intrinsic

cardiac muscle, was noticeable. The process was on the whole a far reaching one, affecting the wall of the auricle at various levels. In other portions there was an ingrowth of strands of fatty tissue between the muscle bundles. Much further down, in the inter-ventricular septum, rather marked fragmentation of the heart muscle had taken place; this lesion is regarded, of course, as a terminal occurrence. Judging from the condition of the transverse striations, there was no parenchymatous degeneration.

Examination of the septum membranaceum revealed a marked increase of the connective tissue at the central fibrous body and in the membranous portion itself, which had undergone hyaline change. Sclerosis, with hyaline degeneration, was indeed the typical lesion of the septum membranaceum, a fact which could be surmised from the gross appearance. The auriculo-ventricular node (Aschoff-Tawara) lay to the right of the central fibrous body. Its general appearance, except for a few dense hyaline connective tissue strands and a moderate amount of fatty infiltration, was normal. Its connection with the auricle was maintained on the right side and dorsally. This junction lay in a bed of fatty tissue. The connection was not so free as is usually the case, though there was no evidence to show that it had been reduced by a pathological lesion. The nodal fibres showed their well-known characteristics; transverse striation was indicated, but much more sparsely than in the muscle of the main stem or in that of the rest of the heart. The small artery usually described as observed in the node made its appearance in the lower portion only.

The main stem of the A - V bundle passed forward in a somewhat oblique direction through the septum to the left. The fibres were well striated. The entire septum membranaceum had, as already noted, an exceedingly dense structure and inroads were made into the bundle by strands of rather dense connective tissue. In addition, and as in the *A - V* node, there was a moderate fatty infiltration of the substance of the main stem. The main stem was further compromised by the presence of large blood sinuses, which seriously reduced the diameter of the bundle. They were large, thin-walled vessels, cut for the most part so as to appear oval, and had a diameter equal to that of four or five cardiac muscle fibres laid side by side. Their long diameters measured from one and a half to twice the length of the broad diameter. There were a number of them in the course of the main stem. They were not accompanied by inflammatory reaction, and if they originated in an inflammatory process, it was quiescent at the time of death. Their importance lay in the fact that the bundle, including the sinuses, had a normal diameter, and that they occupied a space which reduced the normal tissue content considerably. There was an increase in the amount of connective tissue, not only of the septum itself, but within the bundle.

The right branch arose in the usual fashion and presented but a slight constriction at its origin. A few sections below the level or origin, it attained a greater diameter. *The left branch*, on the other hand, presented abnormalities in its origin and possibly also in its course. At its origin a small bundle became separated from the main stem and passed to the left, to lie directly under the endocardium, just anterior to the central fibrous body. This branch could be followed to the end of the serial sections. This condition, namely, early separation of the fibres from the main stem of the bundle, is comparable to what has been described[1] in the *A - V* bundle in cats and rabbits. The left branch at the point of division of the main stem, showed a marked increase in connective tissue. At its origin, it was almost completely isolated from the main stem by the inroads of this tissue. At one level a continuity between the main stem and left bundle was maintained by a few fibres only. At a lower level the left branch regained its normal dimensions. Conduction from auricle to ventricle in this heart occurred therefore through an attenuated main stem, a very deficient left branch, and an almost intact right branch.

To sum up, the lesions presented by this heart included sclerosis and fatty infiltration of the *A - V* node and main stem together with reduction in size of the main stem by the sinuses described ; very marked contraction of the left branch at its origin and some contraction of the right branch. Furthermore, there was an interstitial fibrosis of the auricle and a moderate increase of connective tissue about the nerves and ganglia of the interauricular septum.

A. E. C.

III. *Examination of the medulla oblongata and the vagus nerves.*

The medulla oblongata and the caudal two-thirds of the pons Varolii were received for examination, as well as both vagi nerves and their ganglia. After removal from the body they had been placed for 36 hours in Orth's formol-Müller solution and were then transferred to alcohol. As the tissues had been primarily fixed in a chrome salt solution it was not possible to obtain satisfactory Nissl preparations of the nerve cells, while the time they remained in Müller's fluid was not sufficient to permit staining the myeline sheaths by Weigert's method.

The brain-stem was imbedded in celloidin and cut in serial sections at 15 micra in thickness, and every fourth section was stained by hæmatoxylin and van Gieson's picro-fuchsin mixture. The preparations thus obtained were satisfactory and quite sufficient to reveal any definite abnormality that might be present in either cells or fibres.

The vagi and their ganglia were treated in the same manner.

There was no evidence of any gross lesion in the medulla oblongata or pons ; neither the scar of an old hæmorrhage or softening, or degeneration

or sclerosis of any of the fibre tracts. The cells of the various nuclei appeared undiminished in number and presented no marked deviation from the normal in their staining reactions. In regard to this, particular attention was paid to the cells of the vagal nuclei; they appeared unaffected. The root fibres, both afferent and efferent, of these nerves seemed also, as far as the methods of examination permitted, unaffected.

The only noteworthy change in that portion of the brain-stem that was examined in serial sections was a considerable arterio-sclerosis of its larger blood vessels, and a slight amount of small round cell infiltration into their adventitial sheaths. This resembled that which is often found associated with cerebral arterio-sclerosis in old persons. These vascular changes were irregularily distributed over the sections and bore no local relation to any of the functional areas of the cross-section of the medulla. They were in no place severe, and, as far as could be seen, had not led to any softening or destruction of the tissue around them. The opinion may be safely expressed that they were not sufficient to produce any serious functional disturbance.

No trace of fibre degeneration could be observed in the extramedullary portions of the vagal nerves, and their ganglia presented no abnormality beyond a considerable deposit of pigment in the nerve cells; but this is notoriously common in these ganglia in persons beyond middle age.

G. M. H.

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